THE KGK AUGMENTED RCT©:

Moving the Gold Standard to the Supplement Industry

AUTHORS:

Mal Evans, **PhD, Scientific Director**
Joseph Antony, **PhD, Research Scientist**
Najla Guthrie, **President/CEO**

"Anyone who thinks science is trying to make human life easier or more pleasant is utterly mistaken"-Albert Einstein

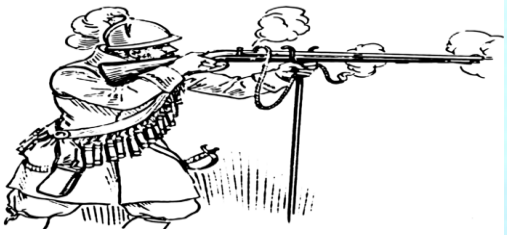
The dietary supplement industry currently finds itself in a similar state of affairs as the nascent pharmaceutical industry decades ago. Despite sophisticated study designs and measurement tools, we are still grappling with the position of nutrients and supplements in the North American health care system. The path continues to be challenging and complicated with research processes tightly bound up in regulations. With focus shifting to personalized medicine, the need to assess the importance of the randomized controlled trial (RCT) and refocus clinical attention from the typical and onto the individual is now in debate. Individuals respond differently to interventions depending on genetic background and environmental exposures. For example, the emerging field of pharmacogenetics aims to identify genetic susceptibility that contributes to inter-individual variability of intervention and certainly plays a role in clinical research. In this context, the role of an RCT as the only method of information for treatment has been and continues to be contentious.

While the randomized double-blind clinical study has ascended as the standard of measurement, understanding the history behind this rise may help unravel the pharmaceutical model for better application to the supplement industry.

From the Battle Fields in 1753 to the 21st Century

The first "digestive medicament" of a novel therapy was arrived at by chance in 1753 A.D by Ambroise Pare, a notable surgeon of the European Renaissance, and regarded by some medical historians as the father of modern surgery. Ambroise, responsible for treatment of wounded soldiers on the battle field, found the supply of conventional treatment to be lower than the number of wounded. He describes:

> "at length, my oil lacked and I was constrained to apply in its place a digestive made of yolks of eggs, oil of roses and turpentine. That night I could not sleep at any ease fearing that by lack of cauterization I would find the wounded upon which I had not used the oil dead from poison. I raised my self early to visit them, when beyond my hope, I found those to whom I had applied the digestive medicament feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses" (an early muzzle-loaded firearm was the primary firearm used in European armies)"[1].



Around the same time and aboard the war-ship *The Salisbury*, after having been out of sight of land for months and with severe dietary deficiencies among the crew, James Lind, conducted the very first clinical study:

> "I selected 12 patients in the scurvy aboard *The Salisbury* at sea. Their cases were as similar as I could have them. They lay together in one place and had one diet common to all. Two were ordered a quart of cyder a day, two - twenty-five drops of elixir vitriol three times a day, two - two teaspoons of vinegar, two - two oranges and one lemon every day and two - an electary recommended by the hospital surgeon. The most sudden and good effects were perceived from the use of oranges and lemons and next were those on the cyder"

Lind's treatise on scurvy, describing a controlled study, was written while he was Fellow of the Royal College of Physicians and showed that oranges and lemons were better than other treatments for the disease [2].

Centuries since these landmark events, the RCT struggled to find its place in a treatment algorithm and has had a contentious history. It gained traction during the pharmaceutical revolution in the fall-out of World War II. In 1943, the Medical Research Council in the UK conducted the first double-blind controlled study to investigate an extract of Penicillin for the common cold [3]. Interestingly, around the same time, Austin Bradford, a British epidemiologist, formalized the RCT. While academic and government services supported RCTs, pharmaceutical companies were against putting resources and time toward them and argued that reliance on testimonials and case reports were adequate [4]. Physicians and researchers looked, to case reports, case series, public demonstrations, testimonials, and occasionally clinical trials to be informed of new interventions.

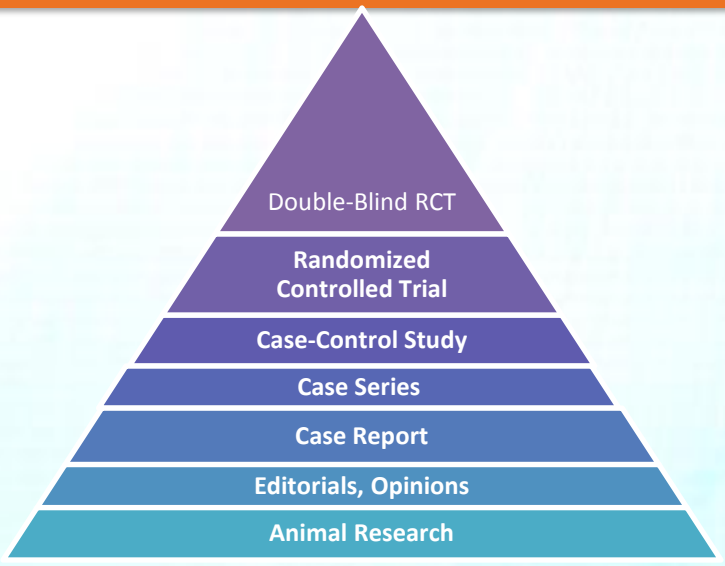
In the years following its formalization, the RCT was initially viewed with concern due to the ethical dilemma of the control group not receiving an intervention. The placebo, a "medicine more to please than benefit the patient" had been identified in 1863 by the US physician Austin Flint comparing a dummy remedy to an herbal extract instead of the established remedy. Others looked to the RCT as a tool of promise in the evaluation process as the tide turned with evidence based on testimonials being considered insufficient and biased. By the 1950s, the US National Institutes of Health joined Britain in funding RCTs. Unfortunately, in the years following, the drug industry remained unregulated; ending only with the tragic consequences of Thalidomide on pregnancy. The Food, Drug, and Cosmetic Act in 1962 mandated proof of efficacy through "well controlled" studies. The US, Europe, Japan, and others implemented regulations requiring RCTs for the evaluation of drugs. During the 60s and 70s, Archibald Cochrane looked to the RCT as a point of differentiation from more liberal study designs.

By 1982, the RCT was firmly established and described as the "standard" to strive for [4], thus setting it apart as "gold" [5,6] and the pharmaceutical industry became the leading sponsor of RCTs [4,5]. In 1979, Boncheck [7] and shortly after, Duggan (1982) [8] , contested the notion of the RCT as the only source of gaining the truth. Further, in 1998, Rene Favalaro expressed concern that RCTs had attained such scientific stature and acceptance that relying on them exclusively was dangerous [9].

Currently the randomized double-blind placebo-controlled trial (RDBPCT) is central to the regulatory process of drug approval. By 2020, it is expected there will be 50,000 RDBPCTs conducted globally per year [10]. However, case series studies, case reports, and big data studying comparative effectiveness on treatment outcomes have continued to inform routine care of patients [11–15]. For example, some surgical techniques were adopted based, not on RCTs, but compelling visual evidence [16,17]. Even though a clinical outcome was the most desirable, it was estimated that 49% of drugs approved by FDA during 2005-2012 were based on "surrogate endpoints" rather than clinical outcomes [18]. This suggests that biochemical changes that may or may not lead to clinical improvements were also found to be sufficient for approval of drugs despite the lack of clinical evidence.

RCTs certainly establish causality through a single descriptive outcome and are relevant in treatment modalities despite a lack of an identified mechanism of action. Most of the low hanging fruit for pharmaceuticals have been picked with crowd-based medicine victories such as vaccinations (e.g. the eradication of small pox) and other population-based interventions [19] and a growing number of orphan diseases (e.g. cystic fibrosis, Lou Gehrig's disease, Tourette's syndrome), restricted to a small portion of the population have become new targets for pharmaceutical drugs.

Evidence-Based Medicine and the RCT



Sackett (1996) who grandfathered the concept of Evidence-Based Medicine (EBM) stated that EBM is the "conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient." He also argued that "good doctors use both individual clinical expertise and best available external evidence and neither alone is sufficient" [20]. Sackett suggested that EBM should not be restricted to RCTs and meta-analyses, and that it was not "cookbook" medicine.

Evidence based medicine requires a bottom up approach that integrates the best external evidence with individual clinical expertise and patient choice. As such, “it should not result in slavish, cookbook approaches to individual patient care” [20].

The application of RCTs to areas of research such as psychotherapy where individualized interventions are “impossible” to be generalized and applied via the RCT have been accepted in treatment modalities [21]. In other instances, the well-conducted gold standard RCTs failed to inform accurately, examples being tolbutamide (anti-diabetic drug) [22,23] and the ALLHAT trial of 2002 on thiazide diuretics [24]. Sometimes, results from RCTs accepted as sound and incorporated into care were found later to be inaccurate or insufficient for reliance [4] , indicating a need to focus on the best available evidence to inform.

Identifying appropriate inclusion criteria compounded by the inability to define relevant outcomes and to standardize interventions were limitations of the RCT [4]. Patients, physicians, and scientists frustrated with the social and ethical concerns of treatment strategies based solely on the evidence of RCTs have demanded more flexible approaches to research [25,26] such as surrogate endpoints and conditional FDA approvals [4]. However, the drug industry continued to champion the requirement of the rigorous evaluation of drugs via RCTs.

Bothwell *et al* (2016) states “even though RCTs were developed to produce generalizable and universal knowledge, they have remained entangled in local social, economic and political conditions” and seem to propel contention. Further, due to their exorbitant cost, achieving positive results and the publication of positive results more often than negative became the focus resulting in an imbalance in medical knowledge [27–30].

Furthermore, physicians still look to alternative methods such as observational studies, meta-analyses, and new forms of studies to make their decisions about treatment modalities. Indeed, though RCTs were originally designed to decrease bias in research, they have become a point of “conflicting interest” [4]. The concept of the “slavish adherence” to prescribed RCT practices was resurrected and was condemned when it caused a “retreat from ethical principle” due to concerns around HIV trials [4,27].

Evidence-Based Medicine vs. Evidence-Based Nutrition - A Roller Coaster Ride?

The application of RCTs to disciplines that are not drug related, such as the nutrition industry, is fraught with problems, the most prominent of which is the inherent differences between drugs and nutrients. Drugs are synthetic and directed towards treatment of disease and

contribute to a one-drug-one-disease concept. They have isolated functions and are designed to target single organs or tissues. Large effect sizes can be expected in drug studies, as there is a true placebo group for comparison. Response time is short and may be associated with large side effects.

Nutrients on the other hand work in complex networks, target all cells and tissues and have multifaceted effects. In the absence of a true placebo group, nutrients have a small effect size and require a long response time. Both drugs and nutrients have different strengths and contribute to the welfare of an individual. However, drugs are therapeutic in nature, whereas nutrients are preventative and are necessary for the optimization of health. Thus, the evidence required to prove efficacy for drugs and nutrients should be different.

Parameter	Drugs	Nutrients
Systemic Function	Isolated	Complex networks
Targets	Single organ/tissue	All cells/tissues/microbiota
Measurement Tool	Single endpoint	Global Index
Response Time	Short	Long
True Placebo Effect	Yes	No
Effect Size	Large	Small
Side Effects	Large	Small
Nature of Effect	Therapeutic	Preventative

Evans et al 2017© adapted from: Blumberg et al. (2010)., Heaney, R. P. (2008)., Shao, A. & Mackay, D. (2010).

Knowing the complex history of RCTs, it is of value to examine their role and application in the nutrient industry. Nutrients are major players in the big picture of health optimization, prevention, and disease risk reduction. The increased life span in the 21st century has also brought the increase in chronic diseases such as cardiovascular diseases, diabetes, and obesity into focus. Furthermore, a change has occurred where instead of standards of care during pre-disease stages, pharmaceutical medications have been introduced. The mechanisms of action and markers of health are poorly established and thus need more comprehensive understanding. In this context, restricting the evaluation of the efficacy of a nutrient/supplement within the environs of an RCT limited to a singleton endpoint is certainly troublesome and needs to be re-evaluated. The rates of investigational dietary supplements successfully exiting an RCT are low while the cost of bringing these compounds to market is escalating. Therefore, novel trial designs are needed and have been proposed to mitigate these effects.

Structure Function Claims and the Regulatory Landscape

In the current regulatory landscape, the highest numbers of claims are made in the structure/function arena. For such studies, the FDA and the European Food Safety Agency (EFSA) require that only healthy populations be studied. However, as healthy people do not typically or consistently present with the indication of interest, the resulting fluctuations become confounders contributing to null results. Furthermore, designing

studies in healthy populations require an understanding of the organ systems contributing to the response and recognition of any external effects that may impact this response. Therefore, enrollment of medically healthy individuals is a challenging task when designing studies for structure/function claim substantiation. However, Health Canada permits the study of pre-disease as well as disease conditions and allows for prevention and risk-reduction structure/function claims.

Disparity in the level of evidence collected from drug evaluations and those possible when examining nutrients has led to the EBM concept becoming a major burden in the application of nutrition to human health [26, 31]. Standards set forth by EBM do not hold up under the unique context of nutrition due to the 'innate complexities of nutrient actions and interactions' [31] and the 'long latency of nutrient-associated diseases' [32] that are difficult to capture using the RCT. Thus, reliance on the RCT has limited nutrition-based policies and advancing this field will depend on finding new approaches that tailor the RCT to the particular properties of nutrients and dietary patterns [31].

In an attempt to stem the epidemic of chronic diseases, treatment modalities are currently being introduced earlier. Previously when pre-disease was identified, normal standards of care were introduced by advocating diet and life style changes. However, standards of care are now dominated by introduction of drugs, and a more recent challenge is that the definition of disease has expanded, with a contemporaneous shrinking of the phase designated as "healthy".

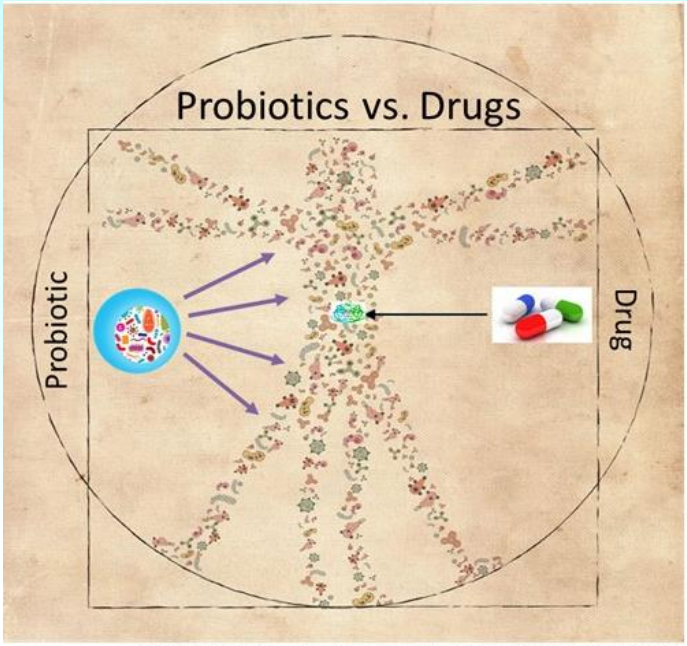
Hypertension Spectrum			
"Healthy"		**Pre-clinical**	**"Diseased or Unhealthy"**
Normal laboratory values	Pre-hypertension	Moderate Hypertension	Hypertension
<120 mm Hg	Systolic BP 120-139 mmHg Diastolic BP 80-89 mmHg	Systolic BP 140-159 mmHg Diastolic BP 90-99 mmHg	Systolic BP ≥ 160mmHg Diastolic BP ≥100 mmHg

Hypertension Spectrum			
"Healthy"	**"Diseased or Unhealthy"**		
Normal laboratory values	Pre-hypertension	Moderate Hypertension	Hypertension
<120 mm Hg	Systolic BP 120-139 mmHg Diastolic BP 80-89 mmHg	Systolic BP 140-159 mmHg Diastolic BP 90-99 mmHg	Systolic BP ≥ 160mmHg Diastolic BP ≥100 mmHg

Nutrients are necessary components of life and therefore contribute to disease prevention. The treatment paradigm is associated with a diagnosis and follows a protocol specifically developed and designed to help alleviate symptoms or decrease/increase levels of surrogate endpoints associated with mortality. A singleton drug theory focuses on minimizing drug-to-drug interactions. At the opposing end are supplements, foods and nutrients that have synergistic or antagonistic effects with each other and with metabolites in the body. Furthermore, the drug model requires an evidence-based system that builds on information obtained from a homogenous population of subjects that is exposed to a treatment. Rigid inclusion and exclusion are used to identify such populations. While this is feasible in a drug-to-disease treatment

model where treatment is the focus, using this as a dietary supplement model is challenging, particularly when dealing with disease prevention where regulatory bodies allow inclusion of only healthy individuals.

A Global Health Index for Nutrients



Adapted from https://medium.com/lsf-magazine/probiotic-philosophy

Healthy people do not present with consistent and homogenous indications that last through a specified period of study. Each healthy individual may respond at a different rate or intensity that may take hours or months to present as an improvement. Personalization must therefore, in some form or manner, be worked into the RCT model. Defined and validated clinical research to put science behind supplements is needed and is not a matter of contention. However, the current mode of study needs to be scrutinized.

The RCT design in this context has limitations when used to evaluate dietary supplements. Safety and efficacy of supplements must be demonstrated but the RCT in its current form is neither suitable nor flexible. As an example, in accordance with the concept of one-drug-one-disease, the drug, Atorvastatin, acts in the liver by inhibiting HMG-CoA reductase. In contrast, food components such as soluble fiber and probiotic supplements, when ingested act on multiple tissues within the body, due to the multi-faceted nature of nutrients (Figure).

The multifaceted nature of dietary supplements and multi-targeted outcomes are not measurable within the scope of the RCT. The RCT model evaluates the intervention based on a one-drug-one disease perspective however; supplements may elicit several positive outcomes that may not be captured in the appropriate setting of a single primary endpoint that is required for substantiation of a claim, thereby deeming the intervention ineffective leading to higher proportions of false negatives. Certainly, health related quality of life questionnaires and several outcome measures may need to be examined to form a global health index that better captures the efficacy of the intervention.

Global indices of health are appropriate in the nutrient realm since functional foods and dietary supplements do not fit into the pharmaceutical model. The intent of the global index would be to capture the improvements that are elicited due to nutrients/supplements

and to solve a health indication; not for statistical convenience. In clinical trials that evaluate the efficacy of a drug, use of a global index comprising multiple single endpoints improves statistical precision, increases efficiency, reduces trial size and cost, and provides trial results earlier [32]. On the contrary, in the nutraceutical industry where health and not disease outcomes are measured, a global index comprising multiple single endpoints, would strive to capture all relevant health outcomes elicited by the nutrient. Identifying a global index that encompasses all these outcomes and sums the effects of a nutrient across systems will better reflect the functional role that nutrients play than from a single outcome measure and may help avoid potentially improper failure of clinical trials due to high rates of type II error (false negatives) [32]. A global index for health may not be a one-size-fits-all and unless the individual components of the index are clinically meaningful, valid, biologically plausible and of importance to the individual, the study may be statistically weakened, and should be reassessed [33].

Conducting clinical trials for the supplement industry comes with a unique set of challenges. Under current regulatory frameworks, the industry must be cognizant in bearing the burden of proof for their marketing claims. EFSA, the FDA, and Health Canada use an evidence-based review system to evaluate the strength of scientific evidence supporting a proposed claim. This review process is heavily based on EBM – a concept with the underlying hypothesis that the intervention ameliorates the condition. EBM aims to integrate the best available evidence into the decision-making process regarding healthcare, and by doing so improving the quality of life for patients [20]. Central to the concept of EBM is the RCT, which permits strong causal inference between an intervention and an outcome of interest [20], and is considered the highest level of scientific evidence able to demonstrate either.

Lessons from the Traditional Chinese Medicine (TCM) Model

The blanket application of RCTs to the dietary supplement and other personalized medicine modals will not achieve the goals of minimizing bias and control for confounding. Disciplines such as TCM have looked to different paths for developing healthcare. A white paper on TCM, in December 2016, highlighted the importance of disease prevention as a cultural goal that has been in place for over 1000 years. The Chinese concept allows for both TCM and Western Medicine to be incorporated together to reduce risk of and prevention of disease and treatment of disease. Several design augmentations to the western medicine model have been proposed and used in the validation of TCM products [34].

Health promotion and disease prevention are the underlying principles common to both TCM and dietary supplements and several transferable study designs, conduct and outcomes of TCM may be applicable to the dietary supplement industry [35–46].

KGK Augmented RCT © Design

The nutrition industry must develop its own standards of proof for EBN decision making. Specific to designing a clinical trial for supplements, foods, etc., the population chosen, endpoints measured, and commercialization goals of the investigational product will significantly impact study quality and the available evidence for claim substantiation [47]. The global health index for nutrients should reflect health rather than disease and can be implemented as the primary endpoint in clinical trials to capture the truly systemic effect on human health [32,48].Further, the model for the supplement industry should not focus on surrogate or substitute endpoints, but on clinically important endpoints. Measurements considered part of the augmented study design should include entry and exit measurement of complete blood profiles, liver and kidney tests as well as recording and reporting of adverse events.

This white paper presents the Augmented RCT® design in order to put science behind the supplement industry. We propose the Augmented RCT® as a better path towards claim substantiation for ingredients and products. We propose a two-stage stratified design [46] incorporating either an open label study or several N-of-1 trials where the results are then extended into an RCT.

In the open-label design the intervention will be provided to all participants. This will be followed by a correlation analysis performed on sub-groups that present with the “most response”, which will need to be defined when designing the protocol to determine responders. The second phase will comprise an RCT where participants who showed an optimal outcome to the dietary supplement will be used in the inclusion criteria and tested against the current standards of care, used by conventional medicine. This will allow for identifying the multi-faceted aspects of the investigational product that will be incorporated as outcomes.

A similar design that would be used as an alternative to the open-label study design will be several N-of-1 trials encompassing numerous participants within a meta-analysis to

provide information for inclusions into the RCT. The N-of-1 trial will use objective data-driven criteria to establish the best intervention for each individual [38], as a particular intervention does not work typically for everyone. The N-of-1 trial has been used in education and learning settings for behavioural and psychological evaluations, physiotherapy, rehabilitation, and in conducting clinical studies for drug use [38].The N-of-1 trial has been deduced from studies to save costs and improve patient management using evidence-based methods, which provides optimal treatment in individuals where there is uncertainty in health outcomes [49].

The Augmented RCT© design allows for more diverse populations to be used in the intervention with relatively smaller number of exclusions required. This study model surely has a place in the dietary supplement industry with interventions and study products that have safety documentation for its ingredients. This will decrease the number of exclusions based on interactions with other medications and supplements.

Appropriate Control Groups for the Augmented RCT©

The “placebo effect”, a phenomenon evident in drug studies, is also very much something to contend with in supplement studies. A large placebo effect associated with a small effect size makes achieving statistical significance unsurmountable and may not be a true reflection of the efficacy of the investigational product.

Broadening our concept of what the correct placebo should be is required. Suitable placebo groups more relevant to the supplement industry would be comparisons against normal standards of care, self-care, or regular medications. These groups would provide for greater generalizability of the investigational products and should be factored into the Augmented RCT© design.

Use of responders has become common practice in nutrition studies, but generalizability of results and their application to claim substantiation has been questioned. Genetic polymorphisms involved in response to dietary supplements could influence the outcome of the study and regulatory precedents do exist for general recommendations based on sub-sets of responders. For example, population wide recommendations, currently in place for reduction in dietary sodium were based on the benefits documented in hypertensive subjects [50] and implementation of folic acid fortification programs based on benefits for neural tube defects in pregnant women [50]. The aforementioned evidence proves that a precedent does exist for nutrition study results in a responder population, to be generalized to the greater population when positioned correctly.

The gold standard randomized control design certainly provides a causal relationship between the product, the outcome, and the associated claim. However, research suggests that the simplistic concept of “one-drug one-disease” evidence required for EBM

does not apply to the unique features of dietary supplements. It is time to augment the RCT to generate evidence required to capture the true potential of dietary supplements.

Cost of Clinical Trials

The cost of an RCT for a drug in the 21st century may exceed $30 million USD, firmly putting such trials only within the scope of industrialized countries [51]. It is estimated that new drug development will cost $1.3 billion USD along with heavy regulatory burdens due to FDA standard phase I, II and III designs [52]. Moreover, the high costs have resulted in the escalating cost of drugs [53].

Despite the cost of bringing a new drug to market, its potential return on investment is substantial given that drugs are patented for 20 years and that their use is well accepted by the populace. On the other hand, the supplement industry does not have anywhere near the same profit margins and bringing products to market from a commercialization standpoint is not currently affordable.

Investing in well-designed clinical studies is necessary. A $100,000 USD study provides the minimum scientific evidence to support the marketing claim of interest where investing more money into science will serve to improve the study in eliciting and establishing the relationship between the outcomes and the supplementation product. It may be argued that the cost of an Augmented RCT© design will be higher than the traditional RDBPCT. However, a study that costs $500,000 USD pales in comparison to fines of several million dollars levied on companies that make sales based on unsubstantiated scientific claims. One may consider the small investment in a properly conducted study as an insurance policy for the dietary supplement industry.

Centuries have elapsed since Pare, Lind and numerous others, demonstrated the value of nutrients in alleviation of disease and suffering. Sackett's words lie heavy upon us as we contemplate the fact that in the 21st century, EBM has in fact become cookbook medicine and has extended to demand similar evidence from the supplement industry. The supplement industry has great potential to optimize health care and to prevent the progress of chronic disease and we need to re-focus on a "bottom-up approach" that encompasses individual clinical evidence to be incorporated into our models of efficacy. This evidence should not be restricted only to RCTs which would certainly only mislead and not inform.

For further information on the Augmented RCT© design, and for application to your investigational products, please contact sales@kgkscience.com.

References

1. Lind, J. A treatise of the scurvy: In three parts. Containing an inquiry into the nature, causes, and cure, of that disease. Together with a critical and chronological view of what has been published on the subject. (Sands, Murray and Cochran, for A. Millar, 1753).
2. D'Arcy Hart, P. A change in scientific approach: from alternation to randomised allocation in clinical trials in the 1940s. *BMJ* **319,** 572–573 (1999).
3. Bothwell, L. E., Greene, J. A., Podolsky, S. H. & Jones, D. S. Assessing the Gold Standard — Lessons from the History of RCTs. *N. Engl. J. Med.* **374,** 2175–2181 (2016).
4. Feinstein, A. R. & Horwitz, R. I. Double standards, scientific methods, and epidemiologic research. *N. Engl. J. Med.* **307,** 1611–1617 (1982).
5. Jones, D. S. & Podolsky, S. H. The history and fate of the gold standard. *The Lancet* **385,** 1502–1503 (2015).
6. Bonchek, L. I. Sounding board. Are randomized trials appropriate for evaluating new operations? *N. Engl. J. Med.* **301,** 44–45 (1979).
7. Duggan, P. F. Time to abolish 'gold standard'. *BMJ* **304,** 1568–9 (1992).
8. Favaloro, R. G. Critical analysis of coronary artery bypass graft surgery: a 30-year journey. *J. Am. Coll. Cardiol.* **31,** 1B–63B (1998).
9. Saxena, S., Weerasuriya, C., Shanahan, F. & Dinan, T. G. *The Placebo Effect: is achieving trial success all in our minds?* (Atlantia Food Clinical Trials Ltd.).
10. Baize, S. *et al.* Emergence of Zaire Ebola Virus Disease in Guinea. *N. Engl. J. Med.* **371,** 1418–1425 (2014).
11. Brasil, P. *et al.* Zika Virus Infection in Pregnant Women in Rio de Janeiro. *N. Engl. J. Med.* **375,** 2321–2334 (2016).
12. Schneeweiss, S. Developments in post-marketing comparative effectiveness research. *Clin. Pharmacol. Ther.* **82,** 143–156 (2007).
13. Schneeweiss, S. & Avorn, J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J. Clin. Epidemiol.* **58,** 323–337 (2005).
14. Varkey, J. B. *et al.* Persistence of Ebola Virus in Ocular Fluid during Convalescence. *N. Engl. J. Med.* **372,** 2423–2427 (2015).
15. Cobb, L. A., Thomas, G. I., Dillard, D. H., Merendino, K. A. & Bruce, R. A. An Evaluation of Internal-Mammary-Artery Ligation by a Double-Blind Technic. *N. Engl. J. Med.* **260,** 1115–1118 (1959).
16. Gruntzig, A. Transluminal dilatation of coronary-artery stenosis. *Lancet Lond. Engl.* **1,** 263 (1978).
17. Downing, N. S., Aminawung, J. A., Shah, N. D., Krumholz, H. M. & Ross, J. S. Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012. *JAMA* **311,** 368 (2014).
18. Feyman, Y. Shocking Secrets Of FDA Clinical Trials Revealed. *Forbes* (2014).
19. Seligman, M. E. The effectiveness of psychotherapy. The Consumer Reports study. *Am. Psychol.* **50,** 965–974 (1995).
20. Greene, J. A. *Prescribing by numbers: drugs and the definition of disease*. (Johns Hopkins University Press, 2007).
21. Marks, H. *The progress of experiment: science and therapeutic reform in the United States, 1900-1990.* (Cambridge University Press, 1997).
22. Pollack, A. The Minimal Impact of a Big Hypertension Study. *New York Times* (2008).
23. Epstein, S. *Impure Science: AIDS, Activism, and the Politics of Knowledge.* (University of California, 1996).
24. Hellman, S. & Hellman, D. S. Of Mice but Not Men: Problems of the Randomized Clinical Trial. *N. Engl. J. Med.* **324,** 1585–1589 (1991).
25. Angell, M. The Ethics of Clinical Research in the Third World. *N. Engl. J. Med.* **337,** 847–849 (1997).
26. Boyd, E. A., Cho, M. K. & Bero, L. A. Financial conflict-of-interest policies in clinical research: issues for clinical investigators. *Acad. Med. J. Assoc. Am. Med. Coll.* **78,** 769–774 (2003).
27. Burdett, S., Stewart, L. A. & Tierney, J. F. Publication bias and meta-analyses: a practical example. *Int. J. Technol. Assess. Health Care* **19,** 129–134 (2003).
28. Zarin, D. A. *et al.* Issues in the registration of clinical trials. *JAMA* **297,** 2112–2120 (2007).
29. Blumberg, J. *et al.* Evidence-based criteria in the nutritional context. *Nutr. Rev.* **68,** 478–484 (2010).

30. Heaney, R. P. Nutrients, Endpoints, and the Problem of Proof. *The Journal of Nutrition* 1591–1595 (2008).
31. Shklyar, I., Pasternak, A., Kapur, K., Darras, B. T. & Rutkove, S. B. Composite biomarkers for assessing Duchenne muscular dystrophy: an initial assessment. *Pediatr. Neurol.* **52,** 202–205 (2015).
32. Sackett, D. L., Rosenberg, W. M. C., Gray, J. A. M., Haynes, R. B. & Richardson, W. S. Evidence based medicine: what it is and what it isn't. *BMJ* **312,** 71–72 (1996).
33. Poon, S. K., Goyal, S., Cheng, A. & Poon, J. in *Data Analytics for Traditional Chinese Medicine Research* (eds. Poon, J. & K. Poon, S.) 1–16 (Springer International Publishing, 2014).
34. Chen, K. Clinical service of Chinese medicine. *Chin. J. Integr. Med.* **14,** 163–164 (2008).
35. Hinman, R. S. *et al.* Efficacy of acupuncture for chronic knee pain: protocol for a randomised controlled trial using a Zelen design. *BMC Complement. Altern. Med.* **12,** 161 (2012).
36. Li, J., Tian, J., Ma, B. & Yang, K. N-of-1 trials in China. *Complement. Ther. Med.* **21,** 190–194 (2013).
37. Lillie, E. O. *et al.* The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? *Pers. Med.* **8,** 161–173 (2011).
38. Macpherson, H. Pragmatic clinical trials. *Complement. Ther. Med.* **12,** 136–140 (2004).
39. MacPherson, H. *et al.* Acupuncture for irritable bowel syndrome: a protocol for a pragmatic randomised controlled trial. *BMC Gastroenterol.* **10,** 63 (2010).
40. Molsberger, A. F., Schneider, T., Gotthardt, H. & Drabik, A. German Randomized Acupuncture Trial for chronic shoulder pain (GRASP) - a pragmatic, controlled, patient-blinded, multi-centre trial in an outpatient care environment. *Pain* **151,** 146–154 (2010).
41. Qi, W. *et al.* Treatment of patients with erectile dysfunction by Shugan Yiyang Capsule: A multi-centered randomized controlled trial. *Chin. J. Integr. Med.* **10,** 96–101 (2004).
42. Satoh, N. *et al.* A randomized double blind placebo-controlled clinical trial of Hochuekkito, a traditional herbal medicine, in the treatment of elderly patients with weakness N of one and responder restricted design. *Phytomedicine Int. J. Phytother. Phytopharm.* **12,** 549–554 (2005).
43. Tong, Z., Yang, B., Chen, B. & Zhao, M. A multi-center, randomized, single-blind, controlled clinical study on the efficacy of composite sophora colon-soluble capsules in treating ulcerative colitis. *Chin. J. Integr. Med.* **16,** 486–492 (2010).
44. Wang, H. *et al.* The key role of Shenyan Kangfu tablets, a Chinese patent medicine for diabetic nephropathy: study protocol for a randomized, double-blind and placebo-controlled clinical trial. *Trials* **14,** 165 (2013).
45. Zhang, C., Jiang, M. & Lu, A. A traditional Chinese medicine versus Western combination therapy in the treatment of rheumatoid arthritis: two-stage study protocol for a randomized controlled trial. *Trials* **12,** 137 (2011).
46. Shane, A. L. *et al.* Guide to designing, conducting, publishing and communicating results of clinical studies involving probiotic applications in human participants. *Gut Microbes* **1,** 243–253 (2010).
47. Heaney, R. P. The nutrient problem. *Nutr. Rev.* **70,** 165–169 (2012).
48. Scuffham, P. A. *et al.* Using N-of-1 Trials to Improve Patient Management and Save Costs. *J. Gen. Intern. Med.* **25,** 906–913 (2010).
49. Gibson, G. R. *et al.* The design of probiotic studies to substantiate health claims. *Gut Microbes* **2,** 299–305 (2011).
50. Petryna, A. *When experiments travel: clinical trials and the global search for human subjects*. (Princeton University Press, 2009).
51. Scannell, J. Four Reasons Drugs Are Expensive, Of Which Two Are False. *Forbes* (2005).
52. DiMasi, J. A., Hansen, R. W. & Grabowski, H. G. The price of innovation: new estimates of drug development costs. *J. Health Econ.* **22,** 151–185 (2003).