“What Did Maxwell’s Equations Really Have to Do With Edison’s Invention?”: Addressing the Complexity of Developing Clinical Interventions for Skeletal Muscle Disease☆

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Abstract

To reach the healthcare market and have a medical intervention reimbursed in any format carries high risk and very low success rates. Even when all regulatory hurdles have been surpassed, there is no guarantee that the product will be purchased; a different body makes that decision using criteria typically unknown to early-stage innovators and intervention developers.

In the context of skeletal muscle diseases, the field is at a crossroads; accurate diagnoses are difficult to obtain, patient management and monitoring are equally difficult, cures are evasive, and disease progression is not well enough understood in the human to identify clear targets (irrespective of whether the specific muscle disease is rare or frequent because the progression is slow and the tissue large). Additionally, the

☆The quote in the title is from the article “A bitter pill,” written by the late Professor Paolo Bianco in 2012, who is missed as both a friend and as a professional medic/researcher who never lost sight of the benefit of fundamental research to human health.
generation of fundamental knowledge stemming from pure academic research, which underpins short- and long-term insight and advances, has been stalled or at least slowed. The field also faces challenges common to all healthcare interventions, while there are also some unique barriers to address, in both developmental translation of the therapeutic and obtaining reimbursement approval. This is independent of the number of people globally who suffer directly and indirectly from skeletal muscle degeneration or degradation. This chapter covers key issues facing skeletal muscle intervention translation, problems that seem to be routinely occurring, followed by suggestions on what can and should be done differently.

1. INTRODUCTION

It is extremely difficult to reach the healthcare marketplace for skeletal muscle disease-related medical interventions, whether they are diagnostic, therapeutic, a medical device, or a care-related procedure or process, and to then have it reimbursed. From the start of clinical development through to market authorization, the healthcare success rate averages only 10% (DiMasi, Grabowski, & Hansen, 2016), without accounting for convincing healthcare providers to purchase the intervention. The underlying issue is that very few people die from the majority of skeletal muscle diseases (Arango-Lopera, Arroyo, Gutierrez-Robledo, Perez-Zepeda, & Cesari, 2013; Kiadaliri, Woolf, & Englund, 2017); primary morbidities such as sarcopenia (Marcell, 2003) or rare neuromuscular disorders infrequently result in mortality because of the muscle disease itself but rather the body suffers an accumulation of strain as muscle tissue deteriorates. Conversely, a large number of common diseases, such as many forms of cancer, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), osteoporosis, and almost all cardiovascular disease, results in skeletal muscle degeneration as comorbidity thereby increasing the healthcare cost (Androga, Sharma, Amodu, & Abramowitz, 2017; Byun, Cho, Chang, Ahn, & Kim, 2017; Fernández et al., 2016; Harada et al., 2017; Von Haehling & Anker, 2014). Therefore, there is a clear and significant health economic impact of damage to the tissue, but in the scheme of decision-making on reimbursing novel interventions, and the present unsustainable nature of health expenditure economics, unless the issue is life-threatening, reimbursement is difficult to obtain.

Obtaining reimbursement is the driving factor for all forms of health care intervention; someone or some entity has to pay for it, and if the costs of the
intervention are not covered, then it is not implemented. As a result, the private sector finds it difficult to focus exclusively on skeletal muscle diseases. This has resulted in an ad hoc patchwork between academia, industry, public funding agencies, and charities/foundations, which at present is only partly succeeding. It is to be expected that if research is financed by private entities, the bottom line will be placed on economic gains rather than patient gains. This focus has generated some poor decision-making and ignores many of the existing and significant knowledge gaps that require a system that promotes fundamental research. It should be noted that these issues are not exclusive to the field of skeletal muscle research; nonetheless, this chapter seeks to outline the present situation and make recommendations regarding where changes can be made.

2. THE INNOVATION SYSTEM PIPELINE LEADING TO CLINICAL INTERVENTION CREATION

Progressive muscle diseases do not lead to rapid death, and during their progression, the accompanying loss of muscle function leads to a decrease in quality of life, and the resultant healthcare costs are exorbitant (Beaudart, Rizzoli, Bruyère, Reginster, & Biver, 2014; Lo et al., 2017). Simultaneously, healthcare bodies, due to financial constraints, are more inclined to address diseases that result in mortality or very high long-term health care costs, which have directly measurable and very large healthcare burdens. The calculations made that underlie reimbursement decisions, based on quality adjusted life years (QALYs for Europe) or disability adjusted life years (DALYs for the United States), are clearer and more conclusive for high direct burden diseases, less so for slow nonmortal degenerative diseases of the skeletal muscle.

Investigators seeking funding who are in academic or research institutes are confronted with the task of proposing a cohesive and timely program coupled with addressing the societal impact of their proposal. For the young investigator, this is as much a challenge as for established investigators; this exercise can result in rather imaginative policy statements. If Gregor Mendel (Miko, 2008) sought funding today to address how sweet pea traits were determined, he would have to justify the work in the context of agriculture and sustainable farming. In the relevance/impact section, he would not be in a position to know that within a 150 years, his data would lead to a revolution in genetics and medicine, and if he were to state such a claim, it is unlikely the proposal would be funded. It is impossible to predict impact,
yet since the Bayh-Dole Act of 1980 (Bayh-Dole Act, n.d.; Rhines, 2005) which has been interpreted to mean that academic innovation has enormous value, such economic and socioeconomic valuations have become a staple of many funding schemes. The Bayh-Dole Act was a US legislation that permitted any entity receiving federal government funds for research to be able to own and commercially exploit the outcomes. Prior to this, any inventions belonged to the federal government if they funded the research generating them. The global impact of this one policy and its nationally mutated versions around the world has been huge. To justify the tax expense of funding public research to the general population, most national-based grants require some level of justification based on a measurable socioeconomic impact. However, the generation of knowledge, whose future value, strategic business case for commercialization, and date of impact are totally unknown, cannot be measured using short-term metrics, because the impact of the generated knowledge may be felt in several generations. The reason we know that the possibility of generating a short-term high impact from fundamental research is low is because we know how much it costs and the probability of successfully translating it into a therapeutic (DiMasi et al., 2016; Sertkaya, Birkenbach, Berlind, & Eyraud, 2014). Such pressure encourages applicants to claim that the proposed research will treat the primary morbidity and might be repositioned for other diseases as a successful healthcare intervention, when in reality this is impossible. As Bianco and colleagues stated in 2013, “A model of ‟translational medicine’ has been subliminally accepted by many scientists. The scheme is driven by the pressure to effect the rapid translation of data from the bench. Translation cannot be aimed for a priori; not everything can, or needs to, be translated” (Bianco et al., 2013).

The value of fundamental research was understood as a result of its impact during the Second World War, which led globally to the creation of tax revenue-based publicly funded research agencies throughout the world (Bianco, 2012): the United States-based NIH and the French-based CNRS are two known examples. The intention was clear, and the generation of knowledge for the purpose of generating knowledge was necessary in itself; it is an indication of a society with a long-term vision when it chooses to investigate the unknown, on the premise that at some indeterminate point, the knowledge will be beneficial. This worked for the best part of 35 years, with the assumption that when knowledge was identified to have a societal value, it would be translated. A very different model to that operating now insists government-funded research must have an identified
societal impact with a route or pathway to it being achieved to justify being funded. However, the impact of knowledge on society is random, which reflects the total heterogeneity and randomness of global society. The instance that predetermination of the application of knowledge is performed, the impact of that knowledge becomes limited because restrictions are assigned to its usage—this arises “when knowledge for knowledge’s sake” is replaced by knowledge for measurable benefit. Knowledge-for-benefit, enforced upon academia as an approach, does not help healthcare simply because the time needed for development is so long as opposed to IT and to a certain extent engineering. In the context of skeletal muscle research, this has created a significant problem. Basically there are a limited number of researchers performing fundamental skeletal muscle research so the knowledge foundation is already limited. There is increasing pressure for funding in the field to perform semitranslational work, irrespective of the fact that there is insufficient information to sustain this approach. It should not be forgotten that fundamental research can and does inform some fairly spectacular advances in life sciences research. One example of this type of advance is the identification of Taq polymerase leading to the development of PCR, which is now used with healthcare research within most molecular diagnostic laboratories. It was not researched with the aim of generating a healthcare benefit but rather stemmed from an initial curiosity-driven project to explore how bacteria grow in hot springs (Brock, 1997). By forcing academic skeletal muscle research to serve societal benefit, it has generated an opposite effect such that the knowledge coffers are not being maintained, expanded, and replenished as quickly as they could. The long-term result is a decreased healthcare benefit.

Only a very specific segment of the professionals on the medical intervention development process fully understand what it means to have a medical intervention launched successfully and correctly within a healthcare marketplace including most importantly that the invention is reimbursed or paid for the potential benefit of patients. To illustrate this point, Fig. 1 represents an industrial standard drug development pathway, ending at generic release. Most life science professionals, irrespective of sector and discipline, are familiar with this image, but will likely not understand it nor the pivotal rules within it. For academic research, the generation of knowledge is not on this chart but rather it is somewhere to the left of it. Without some level of reconfiguration of this innovation cycle, including academic collaboration (Dando & Weiss, 2013), skeletal muscle clinical transition remains problematic. There are several reasons why these problems remain: First,
there is limited flexibility in the animal and human numbers indicated; there are disease specificities, but the numbers correspond to what needs to be performed or engaged to move from one phase to another, with the aim of reaching the final phase adhering to the correct regulations while simultaneously generating statistically relevant data. Statistical relevance in the context of generalizability will be addressed later as the actual physical dimensions of skeletal muscle means that obtaining this one critical point is difficult. The costs of this critical path of translation are actually fairly well fixed (Sertkaya et al., 2014). The issues therefore lie elsewhere. Second, most academic institutes do not have the sufficient expertise and/or infrastructure in-house to do any of this; they are very expensive, have annual maintenance costs, and need to be used significantly to justify their expense. It is not uncommon to witness conversations have held in academic centres with educated specialists in which clinical translation units have been proposed with a suggested composition of the centre consisting of a clinical director and an assistant and the rest is far more poorly thought out but makes for publicity. This naïveté is worrying for the future as it suggests that educated specialists now think that translating their work into the marketplace is straightforward and simple. After 30 years of being told that their research must be demonstrably pivotal with short-term measurable metrics, and after a lifetime barrage of “innovation success” statistics and easy solutions or platforms that facilitate this process, it is likely time to recalibrate. Indeed the popular press has raised concerns regarding the level of nonrelevant academic staff in universities that have nourished a corporate culture in place.

**Fig. 1 Typical drug development numbers.**

![Typical drug development numbers](image)
of an academic one and the potential negative impact (Spicer, 2017). It is clear that other than a small handful of academic institutions, almost all of the rest do not have the knowledge, expertise, financial, or logistic resources required to perform preclinical and clinical translation work correctly. The development of a single intervention might require 1700 mice; however, if this number were proposed in a research grant application, it would unlikely meet with success. Moreover, obtaining the actual license to perform this level of animal work would generate overwhelming paperwork, and many institutes with high animal costs, large numbers of mice would exhaust a standard grant budget leaving not residual funds to pay personnel nor other required reagents.

There are several other knowledge gaps: one key area in the preclinical-to-clinical transition relates to quality control of the intervention being tested in the preclinical phase. Few entities know that regulatory bodies require that preclinical work be performed using interventions manufactured under regulatory and market relevant conditions (current good manufacturing practice or cGMP), to ensure that the manufacturing process does not introduce changes to the intervention profiles, so that the preclinical outcomes can be extrapolated to humans (Plaford, 2015). The cost of these requirements carries a cost between 0.5 million and 2.5 million for the cGMP, ideally the latter because you want enough cGMP product to get you to the end of phase IIa. In the context of biomaterial-based regenerative medicine approaches, this is one of the major reasons experimental concepts do not reach the clinic as scaled-up manufacture results in the loss of the key characteristics of efficacy. In the context of academic research, these points should preclude such work from most publicly funded entities as the resources are simply not available.

In contrast, there are some very innovative models that have been implemented, albeit with varying degrees of success, but with the correct concept, by private charities for some time now, such as Cancer Research UK and their in-house Research and Innovation division (Blackburn, 2017) that successfully bridge this gap and continually strive to find better models to make it work. This will be revisited later, in the recommendations sector with regard to what can be done within muscle research.

The third and final point is that the diagram glosses over some critical issues, specifically late-stage development and the approval phase. What happens during the clinical trial design and implementation, when the trials have finished, how the national health agencies and health insurers perceive the outcome of the intervention, and how they make the decision on
whether to pay for the intervention fundamentally defines the success of the intervention? These issues are relevant equally to all pertinent stakeholders in healthcare intervention design, implementation, and financing.

3. THE RELEVANCE OF HEALTH ECONOMICS AND POPULATION HEALTH IN DECISION-MAKING AND THE COMPLEXITY OF A DEGENERATING MUSCLE

Some of the biggest issues to be contended with for all healthcare interventions are economic based, but unless one has access to a Health Economics studies or Population Health department (Abrams, 2014; EUPATI resources, 2016; Saltman, 2013), has relevant specialists or a dedicated unit, then they will be ignorant of this critical point in any detail. Large pharma and hospitals have these resources, some, but not all, universities have them; it is rare to find them in research institutes and even rarer in small companies. The impact of the economic importance is best understood if the issue is reverse engineered from the process of an intervention being paid for and where in the healthcare system it is being used, back through the precise decision gates that lead to its application, into early-stage academic research. Once this complete path has been identified, to then forward engineer and project manage the process to define who the stakeholders and regulators are, and precisely identify what information and data they require, to then see where optimization, change, and redesign can be implemented to move toward a defined target.

There is a risk during this planning phase if erroneous economic valuations are used to justify the plan: economic valuations are often used during commercially focused grant applications and in the start-up phase of new companies. These valuations rely on an evaluation model call risk-adjusted net present value (rNPV). NPV calculations are standard in business and have been adapted for the high risk long development times of healthcare by introducing a “risk” adjustment; the model aim is to look at the estimated market value of the final product, reverse calculate through the different phases of development, and identify the products present value. If the NPV is positive, then the investment “can” be considered worthwhile. In contrast if the NPV is negative, the investment is considered detrimental. To achieve NPV one has to know the market estimated valuations at each time point, and this works for many businesses with short to medium life-cycles. However, in health, the usage and interpretation of rNPV differ significantly from large industry to early-stage innovators: in large industry the
perception is always long term, using the precise patient population that the anticipated primary endpoint defines, while for early-stage innovators, an abbreviated segment of the plan from above is used. Abbreviated in that estimated final and often total market size of a disease is interpreted to mean the value of the intervention at the end of phase III, and therefore risk calculations mean that phase II has a percentage value of phase III, phase I has a percentage value of phase II, and so on. The error is that final market estimates and phase III data are not synonymous.

In the Fig. 1 scheme, probably one of the largest misunderstandings within many stakeholders is what data is collected during a phase III clinical trial, and how it is used to appraise reimbursement. Common perspectives are that phase III data value is predominantly clinical metric based and that once the data is approved, then its job is done apart from postmarketing control, and just a matter of sales. What actually happens is that prior to a sales force convincing hospitals and trusts to purchase the intervention, it actually has to be approved for reimbursement, and clinical metric data is a small component of that decision approval.

Within the healthcare agencies responsible for deciding whether a therapeutic should be approved for reimbursement, the data is evaluated via a Medical Technology Evaluation Programme, and for the purposes of convenience we will use the National Institute for Health and Care Excellence (NICE) as the model process (Sprange & Clift, 2012); there are some national differences but we will not review them here (another good alternative for educational purposes is the Australian Pharmaceutical Benefits Advisory Committee guidelines) (PBAC, 2015). For review, this typically requires the submission of a reimbursement/Health Technology Assessment (HTA) dossier (Goodman, 2014), which the body reviews as well as performing its own research. The reimbursement bodies look at the scope of the intervention, review the dossier itself which contains information on clinical effectiveness and an estimate of cost-effectiveness based on QALY or DALY calculations, and then generate an appraisal including their decision on if and under what conditions the intervention could be reimbursed.

There are several sections in the HTA dossier and the Scope section has significant relevance for trying to obtain reimbursement for a nonmortal disease-based intervention such as those of the skeletal muscle.

The first component of this section is the target population, and specifically which part of the pathology in this target population the intervention aims to correct; this has direct relevance to the clinical trial design as by phase III the intervention is looking to target a primary outcome (FDA draft
guidance for industry, 2017) of the disease which therefore defines its usage; the intervention will not cure everything, and therefore by definition the agency is only going to reimburse for that defined usage, which then becomes the real market.

The second section is a comparator (Lathyris, Patsopoulos, Salanti, & Ioannidis, 2010; Medina & Alvarez-Nunez, 2011); for muscle diseases this becomes problematic since there are few if any and most target pain and inflammation as opposed to muscle repair. Furthermore the reimbursement agency typically performs the evaluation of an intervention based on it being better and the same price, the same and cheaper or ideally better and cheaper than the comparator, with relevant supporting clinical information. While having a unique therapeutic may seem attractive at the start of an innovation cycle, without a comparator, a lot more clinical data need to be collected to convince the agency, which of course increases the cost.

The third section is effectiveness and quality of life (Piantadosi, 2013): quality of life measurements are made based on a standardized questionnaire or patient reported outcome measure called the Euroqol EQ-5D (Euroqol, 2017) which are completed by the person responsible for interviewing patients during the clinical trial. A sarcopenia disease-specific version has recently been created, SarQoL®, but the authors suggest further validation is still needed (Beaudart, Reginster, Geerinck, Locquet, & Bruyère, 2017). EQ-5D examples can be easily found on the internet, and it is interesting to look at these documents in the context of the level of expense and innovation that has been engaged to get the intervention that far and how this is reflected in a human response. The questionnaire is performed via direct interaction with a patient, and many of the questions are understandably based on the patient communicating how they feel.

For skeletal muscle diseases this creates a significant problem; if this is the primary focus of the intervention, it is likely that the patient has had a slow progressive development of this issue, to which they will have adapted over time and for which there will be day-to-day changes. If this could be supported by additional clinical measurements and/or validated biomarkers, we could envisage generating a comprehensive evidence package of success. However, effective functional and biological diagnostics for muscle integrity are lacking; the standard strength or functional tests such as hand grip strength or walking time and distance are subject to changes based on diet and comorbidities. Biopsies are inconvenient, costly and biased by location of extraction. The absence of precise biomarkers, more effective measurement techniques, as well as management products and processes for muscle disease is inhibiting progress.
The large problem with these assessments are the complications of the comorbidities which are going to significantly influence QALY/DALY assessments, as well as prioritizing which intervention to make. If the patient has heart disease or cancer, and skeletal muscle disease, an economic choice needs to be made: this means the generation of a reimbursable skeletal muscle disease targeted intervention is rather difficult.

The fourth component relates to the components of the HTA dossier: the major component of this is the systematic review (Drummond, 2013; Hart, Lundh, & Bero, 2012) and meta-analysis of the clinical effectiveness. Here, agencies are not only looking at data generated by the manufacturer of the intervention but examine all potential associated clinical trial data, and a confidence interval (CI) analysis (Stevens, 2001) is performed to generate an assessment against the null hypothesis. The null hypothesis is typically that the existing market intervention is better than the proposed new intervention, and it is the design of the clinical trials (patient recruitment, inclusion/exclusion, drop out, and trial structure), which can have a significant impact on defining if the null hypothesis is true, or that there is statistically relevant evidence that the new intervention works.

Note clinical trials, plural, as a CI analysis normally require a significant number of independently performed clinical studies with the proposed intervention (Stevens, 2001): the more trials that have been performed, the greater the possibility that the intervention looks worthwhile.

For most medical interventions, the aim is generalizability (Bonell, Oakley, Hargreaves, Strange, & Rees, 2006; Sculpher et al., 2004), in that any patient can show up with that specific disease at any time point in their life and be prescribed the intervention and benefit from the desired effect. Without generalizability the restrictions on prescription and reimbursement increase, thereby further reducing the market potential. However, the actual physiology and scale of human skeletal muscle tissue itself, how it differs from person to person, age to age, lifestyle to lifestyle, matched with all forms of the muscle degenerative process, makes generalizability difficult to achieve if this is the primary tissue target. If the disease is widespread and a lot of tissue needs to be reached by the intervention, but the intervention only reaches a low amount of tissue then the statistical and physiological relevance of the clinical data generated is consequently much lower. It therefore becomes much more difficult to demonstrate the effect of an intervention in a single human without considering the next step of larger scale usage and generalizability. When routes of administration and dosage requirements are also considered there is a high capacity for adverse events such as nausea and gastrointestinal-related events, again accounting for
height, weight, levels of activity, and lifestyle choices, without integrating in complications arising from the comorbidities.

All of the above points need to be factored in to all stages of the clinical trial design and also back into the early-stage innovation design process. This may read as dissuasive; that is not the aim. The aim is to communicate how truly complicated clinical development and real medical intervention is, and that academia may need to redefine its role away from these routes.

One solution to addressing the complexity would be to integrate Population Health specialists with biological research, which focuses exclusively on knowledge generation could partially alleviate this problem. Population health looks, among many things, at how health outcomes are impacted by societal factors: the environment, lifestyle choices, the economic status of the individual, and the status of the healthcare itself. Surprisingly, the latter has been estimated to be only 20% of the resultant costs of healthcare.

Exploratory and fundamental research generates hypotheses that almost always include a biological component with a human homologue. Whether it is a biomarker or a protein target in many cases there are in many instances human analytical studies published. If population health and earlier stage biological studies are combined, this should reveal human characteristics that could possibly be measured in animal models to generate an expanded insight on muscle degeneration outside of traditional parameters.

If the above work is further stratified by known comorbidities, and then mapped across other muscle pathologies matched with the progressive comorbidities, this should generate significant fundamental knowledge that will permit other specialists to conceptualize and design incremental, progressive, and radical interventions. In concrete terms, from the cardiology, oncology diabetes, rare disease and kidney disease clinic if there are patients with muscle degeneration and another disease, then there will be both differentiators and shared clinical characteristics. There will be potential factors that initiate, amplify, or accelerate disease manifestation; if this information is then replicated in preclinical or exploratory studies using studies of animal models, in which similar morbidity/comorbidity models are used, this will create pivotal fundamental knowledge that maps with the human being. Through this significant amounts of key knowledge will be generated that better informs intervention design and development, now and in 100 years.

The rationale is that to be able to identify avenues that can launch an intervention for skeletal muscle, we have to demonstrate an impact on the comorbidity, which typically means giving the patient more than one
drug, a phenomenon known as polypharmacy. Resolving polypharmacy-related issues (Masoudi & Krumholz, 2003; Stawicki et al., 2015) or considering them as part of the impact on the tissue itself will open new avenues. This work should also be performed with Population Health specialists; if overlaps do appear, it should be determined whether patterns can be identified within a larger animal population, that will provide critical information to correctly choose the animal model for modeling the pathology, and when comorbidities start or accelerate inducing rapid decline define which key mechanisms change when this occurs.

Beyond this point in the path of healthcare design, direct academic researcher involvement in intervention development per se should probably stop. If concepts are going to be transitioned into development, it needs to be done properly, and significantly more fundamental knowledge is necessary for this to proceed. It is not cost-effective for academic institutions to perform this, therefore mimicking other initiatives, it may be time to generate key accelerator laboratories, cofunded and coordinated by charities, with the support of regional funders, national funders, and industry. If the selection process is correct and the work coordinated among the different accelerators to obtain independent reproducibility, this should result in the creation of evidence that permits a potential intervention to be tested and developed. This stated, the process must also be based on a reverse engineering from reimbursement with a clearly defined critical path and clinical study plan.

4. THE PRICE OF FAILURE

The average actual total capitalized cost for drug development is now estimated at $2.6 billion, and insufficient returns are making such expenditures questionable (DiMasi et al., 2016). Since 2010, Deloitte have reported the industry average of returns on investment (ROI) on R&D in the large pharma industry: 10.1%, 7.6%, 7.3%, 4.8%, 5.5%, 4.2%, and 3.7%, each year from 2010 to 2016 (Terry & Remnant, 2016). Stern publishes the different industry costs of capital each year: the 2016 figures, the reported weight adjusted cost of capital for biotechnology drugs and pharmaceutical drugs are 9.25% and 7.58%, respectively (Stern Communication, 2017). The cost of capital is what any provider of funds (bank loan, investor) expects to make from their investment and is calculated to include risk-free returns (bonds), plus a financial risk, plus a business risk. If the ROI is lower than the industry-specific cost of capital it means that by performing this investment,
one is destroying the value of the investment itself making it better to invest elsewhere.

The critical path for clinical development is actually surprisingly cheap: noncapitalized costs of a phase I–phase III trial have been calculated to be $114.2 million, while the direct clinical trial costs of phase I through to phase IV range from $42 million to $118 million depending on the disease (DiMasi et al., 2016; Sertkaya et al., 2014). However, only around 10% of those interventions starting phase I actually make it to phase IV (where on average $6000 per patient per year is required for the marketing control) (Mcquire, 2011). The 90% failure rate is what gives rise to the $2.6 billion cost. DiMasi calculated that the clinical development phase, when accounting for failures, is around $1.4 billion which reflects direct costs added to around $1.3 billion worth of failure, or alternatively when considering why failures occur, this is $1.3 billion worth of knowledge.

Plaford listed the major areas during the clinical development phase where most failure points occur (Plaford, 2015), which were principally linked to misrepresenting the interventions safety profile, insufficient proof of concept data and trial designs inconsistent with clinical endpoints. Most, if not all, of these failure points are due to an absence of knowledge and/or poor decision making. Avoiding these failure points requires a good quality partnership between academia and industry to ensure transparency and foster trust. Ultimately, few want to be responsible for communicating high cost failures. Therefore, publicly funded bodies have an enormous role to play during the clinical development. Failures, therefore, directly contribute to all forms of fundamental knowledge, but they are rarely communicated.

Medical intervention can be schizophrenic: in other sectors, once an idea has been transferred from the public sector to the private sector, all further actions are performed exclusively by the private sector and regulation of that product is based on industrial standards. The purchase of the product becomes a choice of the consumer. For academic innovations based on engineering and IT that do not touch healthcare and in which the innovation has been transferred entirely into the private sector, this results in some world changing innovation. In contrast, within healthcare, the public and private sector perform a perpetual dance, while the stakeholders try to identify key outputs that demonstrate that the field making progress targeting a patient population with a poorly defined market size. There are already many sources providing information on clinical translation that are unnecessary to reproduce. However, Table 1 indicates those that are freely available.
addressing this very complex field, for those that are interested in learning more about the whole process, we also suggest the many reviews and books, which an interested party can easily find in their library. For example, the Oxford handbooks series are rather good on Health Economics and the Economics of the Biopharmaceutical Industry.

It is important to understand in detail the key components that can be obtained from these resources, and tie this information into strategic decision-making and the socioeconomic impact of muscle diseases. It is necessary to consider the socioeconomic relevance of muscle disease because there are few therapies being reimbursed even though the disease range is broad, while the potential to overlap innovation is huge. The future relevance of muscle disease is significantly larger than most people realize, because muscle disease has enormous impact on the changing pertinence of primary morbidity and comorbidity in all diseases and for all ages. This means that interventions need to be designed that target primary muscle diseases as well as diseases that have a significant secondary effect on muscle tissue (e.g., new cardiac drugs will need to demonstrate a beneficial effect on an

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Table 1  Online Resources for Busy Professionals Who Want to Start Learning About Key Aspects of the Intervention Development Process
associated tissue such as skeletal muscle, whereas a cardiac-directed treatment will alleviate the secondary skeletal muscle comorbidity).

Most people suffering from muscular dystrophy die from cardiomyopathy (Van Ruiten et al., 2016). People with cardiac disease have associated muscle wasting. People with cancer, COPD, and diabetes have muscle wasting, as do people with osteoporosis and CKD (Androga et al., 2017; Byun et al., 2017; Fernández et al., 2016; Harada et al., 2017; Von Haehling & Anker, 2014). Aging people with sarcopenia present cardiac comorbidities. These strong associations of diseases are not difficult to understand as the whole body is being strained. As muscle not only serves as a tissue for the body to move but is also one of the largest metabolic “sinks” in the body, muscle will work overtime to maintain body homeostasis. This is important within the contexts of modern health economics such that polypharmacy is a growing problem in healthcare (Beloosesky, Nenaydenko, Gross Nevo, Adunsky, & Weiss, 2013); it induces liver disease, toxic events, and drug failure, and reimbursement agencies now want drugs that impact the primary morbidity and the comorbidity, otherwise it is just another drug to be paid for with questionable efficacy. At any given time, an elderly patient takes, on average, four or five prescription drugs and two over-the-counter medications, and the number of drugs taken increases each decade of life, starting from 50 years of age onward (Flesch & Erdmann, 2006; Lewis, 2017). There is a very real possibility that the efficacy of one therapeutic cancels out the effect of another, with the additional real need to reduce prescription drug costs. This is further complicated by unproven dietary supplements that are routinely used without prescription nor the knowledge of the primary physician that induce metabolic changes subsequently altering the efficacy of the therapeutic, potentially inducing both drug failure and liver injury (Table 2).

Snake oil salesman pitch herbal and dietary supplement remedies that have not been clinically tested (FDA 101: Dietary Supplements, 2017; Roberts, 2017), while other therapies are being pitched and semiapproved for application despite their being little relevant clinical evidence that they work, especially when metrics of therapeutic efficacy are compared to healthy individuals as opposed to placebo controls. Entities whose underlying ethics are honorable can be distorted when shareholder value and publicity risk to outweigh the needs of the patients. These same entities then tie in academic specialists who have been encouraged to seek industry funding in order to demonstrate to the national agencies to justify a model of questionable sustainability. This problem is further exacerbated by an increasing
intimacy between academics and the private that present-day conflict of interest statements do not solve.

Where do we go from here? There are several ways that the problems outlined above can be resolved. There is a growing trend animal work needs to be performed as if it was a clinical trial during the transition phase of exploratory to preclinical work. This means performing animal studies via multisite independent and anonymized or blinded studies to prevent exploratory work that is premature from moving into “development” without being effectively and stringently validated. Additionally, while xenografts and transgenics are good for experimental work, the harsh reality is that they do not always reflect the pathology in humans. One example of this is the mouse model for Duchenne dystrophy that carries the same mutation as

### Table 2 Estimated Global Hospital-Related Healthcare Cost for Caring with Patients With a Skeletal Muscle Disease

<table>
<thead>
<tr>
<th>Primary Morbidity</th>
<th>Worldwide Frequency (%)</th>
<th>Number (Millions)</th>
<th>Number in Millions Who Also Present Muscle Misting (%)</th>
<th>Healthcare Cost ($ Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>11</td>
<td>825</td>
<td>206 (25)</td>
<td>412</td>
</tr>
<tr>
<td>CKD</td>
<td>11</td>
<td>825</td>
<td>74 (9)</td>
<td>148</td>
</tr>
<tr>
<td>CVD</td>
<td>31</td>
<td>2325</td>
<td>674 (29)</td>
<td>1348</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>2.6</td>
<td>200</td>
<td>82 (41)</td>
<td>164</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.2</td>
<td>15</td>
<td>7.5 (50)</td>
<td>15</td>
</tr>
<tr>
<td>Rare diseases</td>
<td>0.02</td>
<td>1.5</td>
<td>1.5 (100)</td>
<td>3</td>
</tr>
</tbody>
</table>

*Note that these values are not “market sizes,” which are defined by primary outcomes but correspond to the healthcare-related cost of caring for patients with muscle disease: to arrive at a market size primary healthcare and patient support would need to be included, and then a detailed cost analysis performed to understand what proportion of those costs are based on medical interventions, which for prescription drugs are only around 10% of costs. Following this one would need to understand what proportion of the population could be targeted and would benefit from the intervention. We have excluded Sarcopenia alone as without doubt there will be comorbidities in the aged, so there will be overlap with the other morbidities. When looking at primary morbidity plus muscle wasting, note that for many of the primary morbidities there are other tissues affected, e.g., in COPD; however, if you were to develop an intervention that targeted the primary morbidity and muscle wasting, this would already be complicated (but worthwhile), however, to generate an intervention to target multiple morbidities would pose unique problems in clinical trial design which would likely prevent any statistically relevant data being generated for the reimbursement agencies to effectively appraise. We are also using western culture healthcare costs, it is very likely that in many other countries the costs are lower, therefore the values are undoubtedly overestimated. For rare muscle diseases we are using figures for all the rare neuromuscular disorders with significant skeletal muscle involvement.

**Facts:** In 2017 the world population is 7.5 billion people.

**Assumptions:** The average minimal hospital-related cost for caring for patient just for their muscle disease is $2000/year, on top of any other medical care.
found in humans (Partridge, 2013). Yet while the mice are not perfectly healthy, they do not die much sooner than unaffected mice and certainly make it to the equivalent of “middle age” in sharp contrast to afflicted boys. If by working with Population Health specialists reveal focus points of interest, which animal models should be used, as well as when and how to better mimic the natural progression of the disease, this will better inform the transition into clinical development.

The prices of failure, and more importantly the knowledge it generates, need to be integrated into the decision-making plan. In and out of skeletal muscle research we are not doing this very well. If clinical development work generates $1.3 billion worth of negative data for each successful drug, then the value of this negative data is significantly greater that its monetary value. The closer we can move clinical development to its critical path value the better it is for all.

Making this happen will be complicated; however, the data is generated for the benefit of private entities within public entities and if pseudoanonymized should be shareable. If we can trade options on negative data like a junk bond, in that be having access to it enables one entity to lower its development cost then revenue is shared or resultant cost reductions result in a financial reward being paid to the provider of the negative data. The more negative data that is shared the more obvious what we should not, but also more importantly what we should be doing with humans with specific diseases.

It should also be possible to use negative data outcomes and map them back into the preclinical and exploratory stages. It is constantly baffling to watch technicians, Ph.D. students, and Postdoctoral fellows work in isolation, present their best data, and get a publication. Yet no one shares avenues or techniques that did not work or were not worthy of a high impact publication. Put in a different context, if all the muscle charities insisted that the work they support also share negative outcomes on a centralized database, new avenues of research would be much better informed this is critical when one considers that 95% of fundamental research results in disproving a given hypothesis, and these results are subsequently not communicated. Significant duplicated efforts would be avoided is such information was shared.

5. CONCLUDING COMMENTS

The reality within all of healthcare is that it is caught in a cycle of increasing costs and needs and that budgets to address this situation are decreasing. The large pharmaceutical model is only viable providing
healthcare systems reimburse their interventions and healthcare systems are viable providing they reduce costs and maintain health. Caught in-between are academic entities generating knowledge along with charities trying their hardest to support patients and their families. From a strategic perspective, the field needs to redesign the risk assessment and management controls, optimize the portfolio designs, and tie in all stages of intervention development with the clinical need to fundamentally reset the clock. Roles and responsibilities of all the actors need to be redefined as a function of the knowledge gaps. This needs to be implemented transparently such that all failures are identified as early as possible and communicated whether their source is private or public. In parallel, national governments need to rededicate their commitment to “generating” knowledge and reconsider the viewpoint that research investment is somehow directly linked to curing a specific disease as well as stimulating the economy, at least in a manner that is under their control. In the case of skeletal muscle disease, there needs to be a significant increase in knowledge creation and availability, for the exclusive purpose of creating that knowledge and providing insight, prior to any further translational steps being taken. This will require integrating our knowledge of the tissue, its biology with population information, and major decision-making structures to accelerate new therapies.

Development of medical interventions for skeletal muscle diseases is necessary; skeletal muscle degeneration plays a key role, from rare diseases in children through to octogenarians who are major sufferers of muscle function decline. As few people actually die from skeletal muscle degeneration directly, it poses a conundrum for clinical development of therapeutics, especially in the context of how healthcare reimbursement decisions are made. Because loss of muscle function has a clear negative impact upon the quality and length of life when copresenting with other morbidities, and children with rare diseases die from those morbidities, it is without question, worthwhile to pursue this line of research. With correct planning and a collective fundamental shift in how all forms of data are perceived as well as a recognition of the value it generates, in light of the unsustainability of existing healthcare infrastructures, this change may result in alleviating costs and offering solutions that so far have been difficult to identify or envision.

REFERENCES


FURTHER READING


