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Stage-gate process for life sciences and medical innovation investment

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ABSTRACT

Life science innovation has led to significant improvements in clinical outcomes and has been a source of financial growth for individuals and institutions capable of performing appropriate investments in this sector. Several groups have developed methodologies to assist medical technology innovators in the design and development activities. Unfortunately, these tools have not aided the general investment community to profit from these enterprises. This situation has contributed to a general reduction in risk capital directed towards life sciences compared to other industries. We review the current investment practices in the life science sector and present a comprehensive stage-gate model that aims to captures this investment process. An analysis of best practices and in-depth interviews with 68 life sciences investors and entrepreneurs worldwide are used to support such model. A single case-control study comparing life science investment execution within two similar investment firms was conducted to evaluate feasibility in the implementation of these practices. The stage-gate model includes (I) General vision and investment strategy definition; (II) Venture search, screening and rapid pre-evaluation; (III) Due diligence and negotiation of terms; (IV) Portfolio management, evaluation, and exit. The difference in execution of investment and results from a post-performance Root Cause Analysis were consistent with a reduction in perceived risk from the case company trained with the proposed model compared to the control. This suggests that our developed model and process may be useful in encouraging life sciences investment via evidence-based evaluations.

1. Introduction

Over the past two centuries, medical innovation has dramatically changed the way we manage, treat and perceive disease (Brodsky, 2010). Consequently, it has been through appropriate technology development that clinicians, engineers, and scientists have enabled millions to live longer and, to a certain extent, healthier lives (Fuchs and Sox, 2001; Grimes, 1993). Hundreds of biomedical advancements have since taken the form of new procedures, compounds, tools, policies or guidelines, many of which have even become standards of care in the last decades (Bauchner et al., 2016; Howell, 1996). Consequently, medical innovation has proven to be not only necessary for society, but also an increasingly valuable economic activity (Cutler, 2007; Porter, 2010; Webster, 2002), capable of becoming an attractive basis for ambitious businesses (Drucker, 2014).

In general, life science products such as medical devices, pharmaceuticals, biologicals and biotechnological systems are commercialized within a highly regulated and multidisciplinary environment (Maak and Wylie, 2016). This situation has certainly defined a range of product development processes unique to this industry (Curfman and Redberg, 2011) fields. Among these models, the so-called Biodesign process (Zenios et al., 2015) has become a hallmark in medical devices and life science entrepreneurship. This process has become increasingly relevant for development teams as it presents useful strategies to guide technical activities and milestones in the pathway to commercialization of life-science technology, from ideation to market deployment. Consequently, Biodesign-like courses in academic and research settings are now offered more frequently than before, which has also encouraged public and private sponsors to embrace the idea of enabling social impact by supporting student-generated life science ventures (Asch and Rosin, 2015; Sinha and Barry, 2011).

Despite the many positive consequences that the development of the Biodesign process has brought to the life science innovation community, its value to inform prospective investors regarding best practices in the selection of promising ventures is questionable. This gap is especially apparent during evaluation of early-stage investments, where substantial additional resources are required to complete product development, clinical testing, regulatory approval, and commercializa-

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tion, all of which are necessary milestones to confirm market potential. Indeed, previous stage-gate models in life-sciences pertain primarily to product development activities and do not provide enough guidance to prospective investors on how to conduct other critical activities such as the filtering, selection, negotiation, and management of life-science ventures. Furthermore, convenient tools to formally evaluate promising life science investment prospects are virtually absent, and specific guidelines to perform other important tasks such as early-stage valuations in this sector remain largely unaddressed (Girling et al., 2010). Consequently, the process of executing private investments in the life science sector continues to be tedious, complex and particularly heuristic (Ioannidis, 2015a). This situation emphasizes the need for intuitive models capable of mitigating investment risk, through the dissemination of the general principles that define a successful life science investment cycle.

The lack of representative models and efficient risk mitigation strategies for life science investors is a critical gap capable of negatively impacting capital investment in this industry. For example, a recent study evaluating US investment trends from 2010 to 2015 observed a 15.8% decline in all-stage life sciences risk capital as a percentage of total investments, with the most significant reduction in capital injection being attributable to early-stage healthcare projects (Fleming, 2015). This decrease in life sciences investment has occurred despite a 95% increase in the total amount of venture capital injected across all other US industries totaling $39.6 Billion in 2015. Indeed, investment decline is usually a consequence of changes in risk perception. Several national and international metrics in medical research confirm the existence of significant gaps that limits the translation of scientific discovery into clinical and economic value (Moses et al., 2015). These observations are consistent with a perception of higher investment risk.

Considering that the investment community is currently shifting away from life sciences to other sectors, as well as within life sciences from early stage to late-stage investments, it is critical to understand the root causes of these changes to implement reforms capable of reversing it. The typical hypothesis explaining life science investment shifts proposes that medical technology investment has just become riskier over the years due to increased regulatory scrutiny and other market constraints (Bergsland et al., 2014; National Venture Capital Association, 2013). Ironically, it appears that innovation in life sciences happens much more frequently and within a much more informed framework than ever before (Collins, 2015; Holmes, 2016). This situation should reduce the risk for stakeholders, suggesting that current investment shifts are not only attributable to lack of promising projects or stringent market hurdles, but also to a mismatch in risk perception among investors and entrepreneurs.

The presence of numerous life-science products reaching commercial success every year shows that it is at least possible for informed investors to profit from entrepreneurship in this sector (Fernald et al., 2015). Therefore, it is desirable to understand how these groups can identify medical innovation with enough potential to be translated into successful ventures. Elucidating this process is paramount to revert declining life-science investment trends, enhancing the ability of these companies to create value. Providing clarity in this investment process will also help innovators account for the investor's risk while navigating through the regulatory, reimbursement, and clinical hurdles while keeping reasonable timelines and budgets. Here we aim to investigate the general process of life science investment, and to propose a simplified model to inform potential investors regarding best practices and an effective toolkit to democratize these opportunities.

2. Methods

The purpose of this study is to present a comprehensive stage-gate model of life science investment developed through in-depth interviews with 68 life sciences investors and entrepreneurs conducted between April 2014 and April 2016. Selected interviewees (ages 46.6 ± 10.8 years) had at least seven years of prior experience in life science investment activities and comprised senior professional staff from angel investment groups, venture capitalist firms and technology incubators based in the United States, Europe, Latin America, South East Asia and the Middle East. The interview process was conducted in agreement with a previously reported methodology (Pietzsch et al., 2009) used to inform medical device design and development processes, but adapted to generate a framework useful for investors. Unstructured interviews were the primary source of information used throughout this investigation. Despite its qualitative nature, this particular interview process was selected to add flexibility in the questioning of interviewees during the discovery and definition of our investment model. Furthermore, an unstructured interview format is a standard approach in the investigation of many unknown processes, which can lead to more comprehensive process descriptions than those potentially generated from structured interviews, which do not allow for clarification and additional interrogation of interviewees. All interviews were conducted remotely (via telecommunication) by two interviewers based in Boston MA, USA, and Mexico City, Mexico respectively, and comments were captured continuously during each interview session.

Apart from the previously described interview process, other experts and key opinion leaders from relevant stakeholder groups were also consulted during the drafting, evaluation, and refinement of the proposed investment model after interviews were already conducted. These experts were independent of the investors and entrepreneurs interviewed for this study and included executive personnel from early- and late-stage life science ventures that were involved in at least one capital investment event within the year preceding the study. Other consulted experts included hospital administrators, physicians, regulatory strategists, reimbursement advisers, insurance representatives, as well as managers in charge of product development, engineering, clinical testing, manufacturing, marketing, and sales of medical devices, pharmaceuticals, biologicals and in-vitro diagnostics. The role of these informal consultations was to provide clarification of terms, conditions and activities reported during interviews.

After interview responses, had been collected, all available information was analyzed to generate hypotheses regarding the underlying activities involved in successful life sciences investment. These activities were included in our model definition and included specific evaluation events leading to risk reduction, as well as stage gates acting as milestones leading to investment execution. The draft model was presented to interviewees to be revised and improved iteratively. This methodology followed a well-established research technique known as grounded theory building (Corbin and Strauss, 2014) that can be used to describe complex phenomena such as investment processes from a combination of empirical assessments (e.g. structured or unstructured interviews) and previously available information from literature (Pietzsch et al., 2009). A schematic showing the sequence used in the conduction of these interviews, as well as the structure of the initial and secondary phases of assessment is presented in Fig. 1. Columns in Fig. 1 denote the type of interviewed investor, while rows denote the different rounds of interviews. Boxes and parallelograms indicate specific activities in the interview process. Convergence in the model was measured by a reduction in requests for change between assessment rounds.

The sequence of tasks performed to construct, revise and refine our proposed life science investment model comprised the following activities:

a) Initial evaluation of life sciences investment practices and available standard operating procedures (SOPs) from eight interviewees actively involved with angel, venture, and corporate investment groups.
b) Identification of functional groups of experts, advisors, and consultants involved in the evaluation of prospective investments.

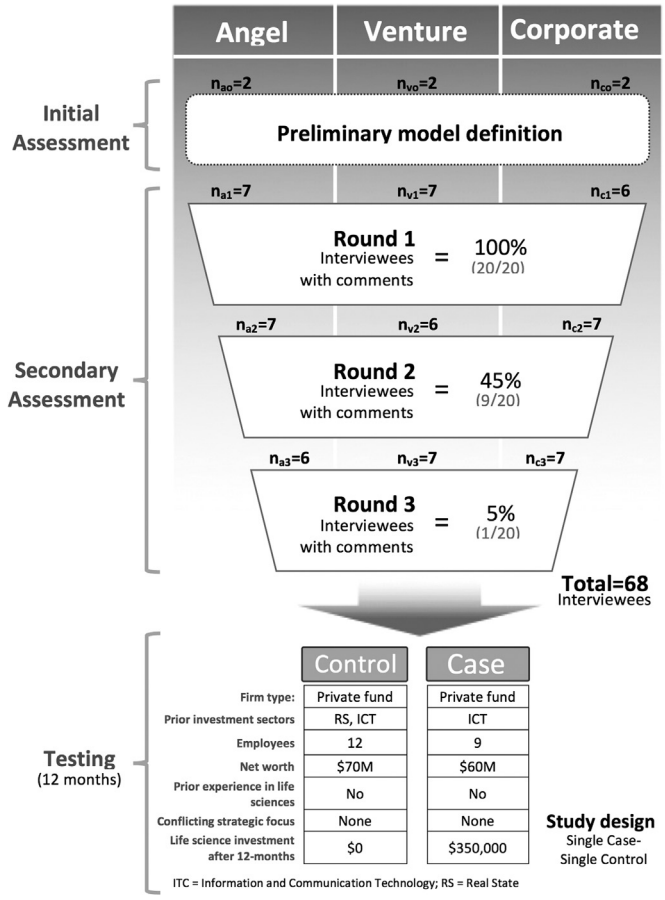

Fig. 1. (Top) Interview process used to define our proposed life-science investment model. Columns denote interviewed investor type, while rows denote the different phases of the assessment. Boxes and parallelograms indicate specific activities in the interview process. Subscripts in number of interviewees indicate investor type (a = Angel, v = Venture, c = corporate) as well as assessment phase and round. For example, na1 = 7 indicates that seven angel investors were interviewed in the first round of the secondary assessment phase. A reduction in the percentage of interviewees requesting changes throughout secondary assessment indicated a convergence in the model. (Bottom) Chart of case and control firm characteristics. Both firms confirmed no previous experience in life science investment and were active investors in other sectors. A single life science investment was executed by the case firm during the study, the control firm did not execute any life science investment during that same period.

c) Based on this initial assessment phase, we identified potentially critical steps, activities, actors, and decisions involved in a single investment cycle.
d) The preliminary life sciences investment model was drafted using these identified elements.
e) The developed draft was presented to a total of sixty new interviewees in three independent rounds during the secondary assessment. Evaluation and refined of our model were done based on feedback from respondents, in the form of suggestions and requests for change. Requests for minor modifications in each round were applied continuously to be assessed by subsequent interviewees. Major requests for change were only implemented after the conclusion of each interviewing round and upon confirming consensus among respondents. Interviewees with no comments or requests for change were asked to confirm full agreement with the presented model. A significant decline in the number of petitions for change per interviewee was indicative of model convergence reaching 5% by the end of Round 3.
f) Upon convergence and revision of the life sciences investment process, a rapid pre-evaluation checklist was also created using the information obtained from these interviews. The generation of this pre-evaluation tool was not the primary objective of the conducted interviews and only constitutes an auxiliary instrument that we consider potentially valuable for new life science investors. An example embodiment of such checklist is presented in the supplemental material of this work, and its use and objective will be described in further sections.

After the generation of a converged life-science investment model, we aim to conduct a limited 12-month single case – single control study as a proof-of-concept to test feasibility in its implementation. In this experiment, two similar but independent investment firms located in Mexico City were tracked to assess differences in investment behavior when trained in our developed model. Inclusion criteria for these investment firms comprised: 1) Confirmation of the desire and capacity to execute life sciences investments within the duration of the study, and 2) No previous experience in life sciences investment. Exclusion criteria included: 1) Firm's bankruptcy; 2) Conflict of interest in life science venture selection; 3) Predefined focus on a particular disease or vulnerable population, and 4) Expressed desired to leave the study. The first two investment firms confirming inclusion criteria were selected, and a simple randomization process was conducted to select which company would act as the case, rendering the other our "control. The staff in the case investment firm was trained through an 8-h session on the generated life science investment model, and then followed throughout the duration of the study to observe implementation. The control company was not assisted nor informed of the existence of a life sciences investment model and was only followed to throughout the evaluation period to confirm the ongoing intent of executing life sciences investments.

3. Results

To our knowledge, the presently developed stage-gated model constitutes the first attempt to fully characterize the complex and often iterative life science investment process. The presented investment model was linearized to simplify representation and execution according to interviewee comments and suggestions. Relevant elements of this model are further explained in following sections:

3.1. Stage-gate investment model

Our proposed linear model (as shown in Fig. 2) identifies relevant functional groups interacting through four major phases, separated by three decision gates. In this model, each stage depicts a series of essential activities performed progressively to reduce uncertainty and risk for the prospective investor. Upper-level activities were defined as with higher priority than lower ones. The horizontal progression represents a general timeline of a single investment cycle. The four most important phases with their corresponding decision gates include:

- Stage I/Gate 1: General vision and investment strategy definition. This phase concludes with the documentation of such strategy and the formation of a life sciences advisory network to assist in the venture evaluation process.
- Stage II/Gate 2: Venture search, screening, and rapid pre-evaluation. This step culminates with a list of highly ranked life sciences investment candidates, as well as the execution of all the agreements necessary to perform due diligence on these companies.
- Stage III/Gate 3: Due diligence and negotiation of terms. This phase starts with the request for an investor's package for analysis and finalizes when investment is executed on the basis of analyzed evidence.
- Stage IV: Portfolio management, evaluation, and exit. This is the final, but perhaps lengthier phase in the life sciences investment cycle. It assumes control in all portfolio additions and management using quantitative metrics to evaluate performance. This stage concludes only after an exit event.

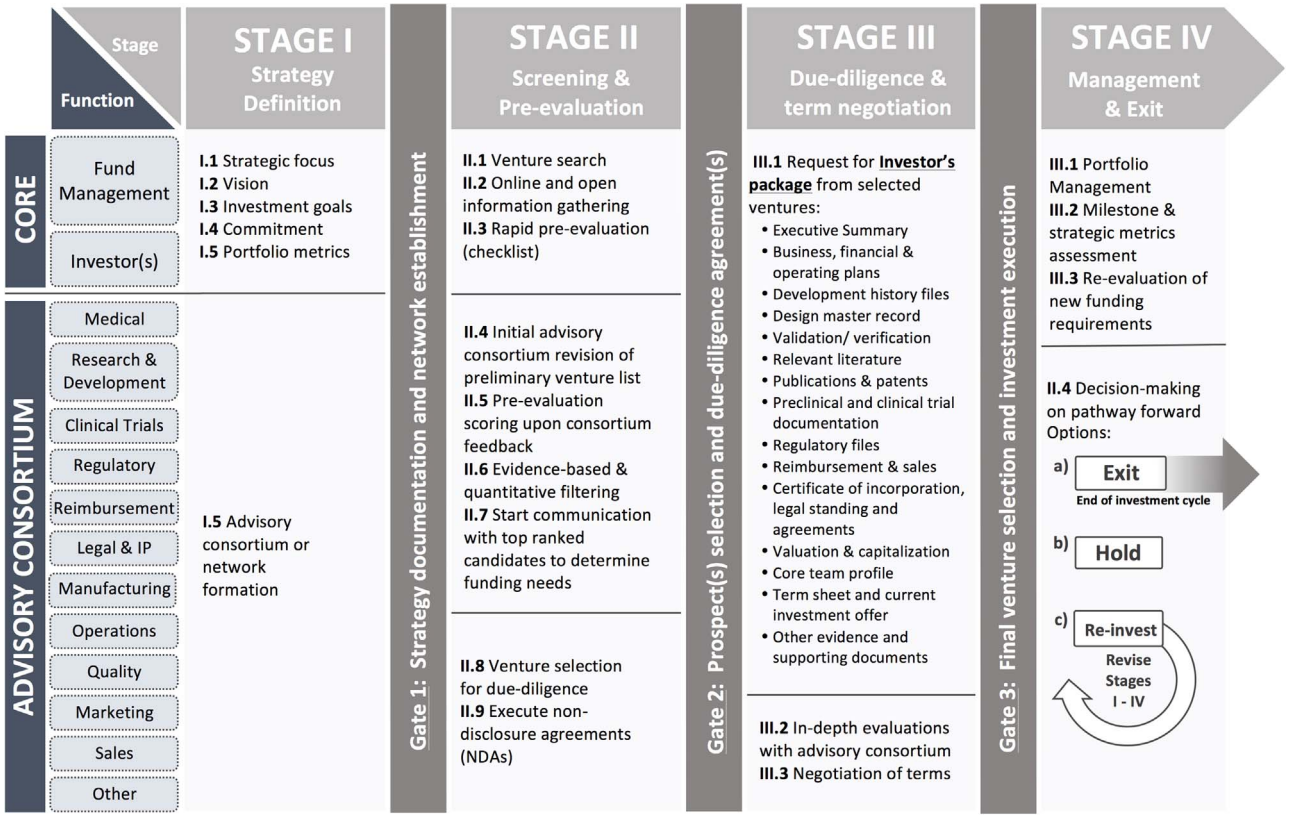

Fig. 2. High-level representation of relevant phases and activities in the life-science investment process. Columns in this linearized model represent stages separated by gates. Rows indicate functional groups and process activities. IP = Intellectual property.

3.1.1. Strategy definition

It is highly recommended that prospective and recurring life sciences investors unambiguously frame their investment goals, including expected financial commitments and desired metrics to assess portfolio performance. Such parameters may include: investment amount, portfolio size, return on investment, the number of liquidity events per investment cycle, exit time, the number of newly serviced customers or patients, and the number of jobs created to mention a few metrics. Life sciences investors are also encouraged to state their overall vision for this investment process openly. It is not uncommon for high net-worth individuals with limited experience in life-science investment to push for life science investment having a target disease or vulnerable population in mind. If not carefully structured, these paradigms could narrow the number of assessed investment opportunities and could ultimately limit the investor's ability to profit from these activities. A knowledgeable life sciences evaluation expert should not underestimate the importance of tacit expectations and unformulated investment visions, as they may become a root cause of wasted efforts. High-level assessments regarding significant local or international gaps in healthcare access and delivery may guide the definition of promising targets for strategic focus in each investment cycle. In any case, it must be considered if a particular target area has been pre-selected without analysis, or otherwise to prevent evaluation of ventures that do not fit the user's investment thesis.

3.1.2. Venture search

After defining a proper strategic focus, prolific life science investors usually conduct quick screenings of as many suitable prospects as possible. It suffices to say that many impactful and potentially disruptive life science ventures often spun from prestigious universities as well as medical research institutions, so collaborating with these actors may improve the likelihood of finding attractive options to invest. Performing a comprehensive, updated and fruitful venture search may appear daunting for many, especially when considering the increased popularity of stealth medical research (Ioannidis, 2015b). Fortunately, many simple and cost-effective strategies can be used to facilitate these searching activities. Such is the case of innovation intelligence resources (e.g. Thomson Reuters's Venture Economics database), auto-generated online news alerts (e.g. Google alerts) and other large-scale fetching tools, all of which are increasingly used by venture capitalist to find suitable investment opportunities. All the previous approaches combined with attendance to scientific conferences, business plan competitions and traditional scouting of highly cited projects published in renowned databases or journals (i.e. PubMed) can provide a highly informed picture of the current life science entrepreneurship landscape without unreasonable time commitments from evaluators.

3.1.3. Life sciences advisory network

Several healthcare-only incubators, consortiums, syndicates and investment groups, usually operate under the assumption that life sciences investment requires unique kinds of expertise to be conducted successfully, at least compared to other less regulated industries. Indeed, the extent of clinical, scientific, regulatory and engineering background required to conduct accurate life sciences venture assessments may pose a challenge for less informed evaluators and small investment groups without any Biodesign training. In many cases, building the internal capabilities to conduct required evaluations in-house may not be possible and can constitute a significant barrier for new investors trying to enter this sector. Although some expert advice is almost always needed to reduce uncertainty to acceptable levels during the venture selection process; in most cases, these activities happen rather sporadically and can be performed on an ad-hoc basis by external consultants. This situation allows for evaluations to be assisted or even entirely conducted by an external advisory consortium or expert network, which can be an attractive and cost-effective platform to

meet these assessment requirements. Based on our interviews, a well-constructed life science advisory network should comprise the following experts:

- Seasoned medical technology entrepreneurs.
- Practicing clinicians, nurses, and other medical personnel.
- Published researchers and academics actively working in the field of interest.
- Medical device and pharmaceutical regulatory experts.
- Reimbursement, insurance and pricing consultants.
- Government officials in local ministries of health.
- Intellectual property lawyers.
- Quality assurance specialists with experience in medical technology development.
- Industry and manufacturing experts.
- Electrical, mechanical, chemical, biomedical and software engineers.
- Representatives from patients advocate groups.

Access to such networks can be facilitated through collaboration with local academic institutions, incubators, research societies and medical centers with established programs to train entrepreneurs in life science technology development and commercialization. Several academic groups such as the Stanford Biodesign program (Brinton et al., 2013; Yock et al., 2011), and the Johns Hopkins Center for Bioengineering Innovation and Design (Yazdi and Acharya, 2013), are but a few of many successfully implemented programs that have developed such networks.

3.1.4. Life sciences pre-evaluation tool

Since the identification of a large number of well-defined ventures is usually desirable to increase the probability of executing profitable investments, the life science investor also needs to be particularly skilled in filtering down these various findings into the most promising prospects. The use of rapid evaluations is usually the preferred method to accomplish this filtering task. Risk mitigation in this phase of the life science process demands that investment screening gets conducted as quantitatively as possible, considering moderate time investments.

However, tools to assist investors in filtering promising life sciences investment prospects rapidly are virtually absent (Campbell, 2012). In this sense, the so-called health technology assessment (HTA) (Battista, 2006) is perhaps one of the few potentially available options for investors to perform structured life science evaluations for this purpose. In general, the HTA process is a method capable of estimating technological safety, clinical efficacy and even market adequacy in absolute and comparative terms, all of which is conducted in the context of the many regulatory and reimbursement barriers for medical products (Perry, 1999). Although HTAs are indeed valuable in a broad range of life science evaluations, current HTA implementations are not considered rapid assessments and require the compilations of extensive pieces of evidence to provide useful conclusions regarding the expected value of a particular life science technology (Khangura et al., 2014). Furthermore, HTAs only focus on the technology itself and may not necessarily evaluate other relevant aspects determining the success of life science ventures. These and many other gaps in such available evaluation tools constitutes an unforeseen barrier limiting the ability of investors to perform rapid life science investment screenings.

Throughout our interview process, we have identified that having access to a quick pre-evaluation tool is a highly desirable condition for investors to facilitate venture selection and to justify any capital- or time-intensive efforts to validate promising investment opportunities. Any potential embodiment of such tool should maintain the search process as dynamic and as inclusive as possible while optimizing time with the resources available to the investor. We have identified that a useful pre-evaluation tool should meet the following criteria: 1) Can be rapidly defined and adjusted continuously; 2) Is self-explanatory and simple to use; 3) Can be completed with public and non-confidential information; and 4) It generates a quantitative or semi-quantitative output score that is representative of the expected value of an investment prospect. Considering these requirements, we concluded that a weighted closed–answer questionnaire or "checklist" would likely be an ideal format to perform this rapid pre-evaluation. A simplified schematic showing the process used to generate our proposed pre-evaluation tool is presented in Fig. 3, and an example embodiment of

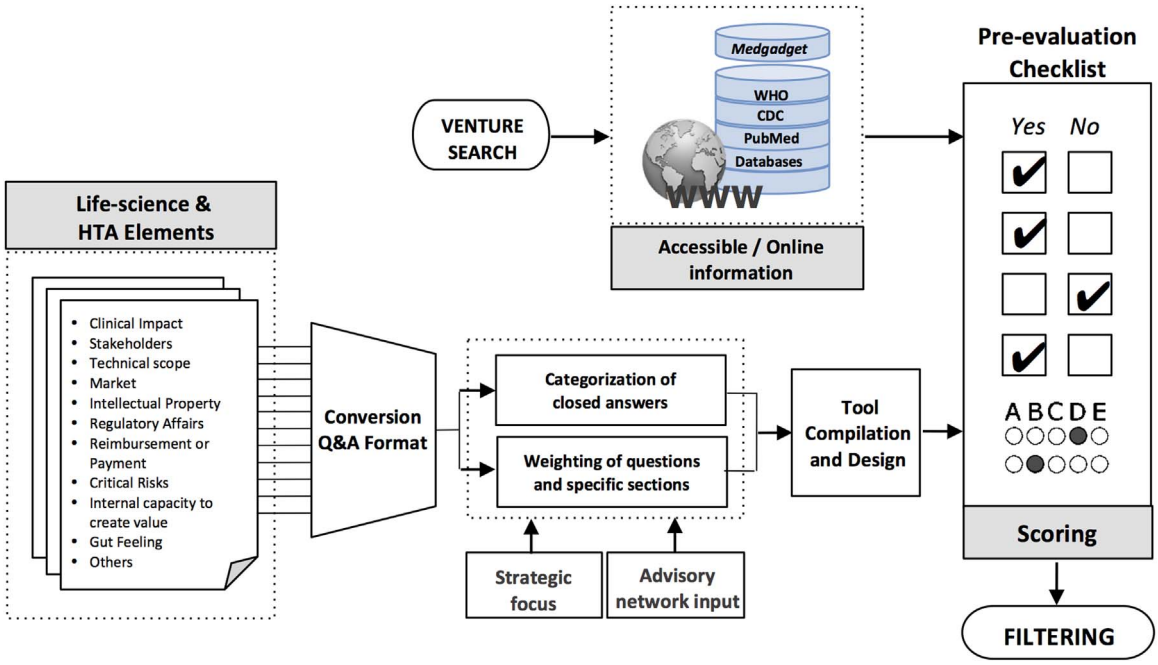

Fig. 3. Process used to define a rapid pre-evaluation tool for life-science investment. Biodesign and HTA elements are used to create a questionnaire. Inquiries and potential answers to this questionnaire are categorized and weighted according to specific strategic focus and life science expertise available to the user. The preferred embodiment of this tool is a checklist which allows for rapid quantitative analysis and comparison of evaluated investment candidates. (CDC = Centers for Disease Control and Prevention of the United States; HTA = Health Technology Assessment; Q & A = Questions and Answers; WHO = World Health Organization; WWW = World Wide Web.).

such instrument in the supplemental material (Zenios et al., 2015).

Our life science investment pre-evaluation is intended to quantify the degree to which a medical technology venture meets pre-defined investment criteria, guiding screening decisions using readily available information. To generate our example tool, we have selected value generating elements from the Biodesign process (Zenios et al., 2015) and HTA items that are considered critical to reduce investment risk (e.g. high clinical impact, ease of regulatory pathway, known reimbursement coding, etc.). These elements were then weighted using input from interviewees and placed in a checklist format. In case the potential investor wants to construct an alternative pre-evaluation tool, careful consideration must be taken to include all desired items through succinct inquiries ideally in a closed-answer format to ease data collection and scoring. Also, feedback from every particular advisory network must be taken to define these criteria, as well as weighting, and scoring. Typical evaluation elements that are usually presented with the highest scoring weights are: Intellectual property landscape and Potential regulatory pathway, due to the significant commercialization barriers that might arise from these specific conditions. Finally, an optional element that may be incorporated into this tool is a "gut-feeling" or "intuition" section, which could be filled by key opinion leaders in highly speculative markets or when evaluated information may not be reliable. Once a particular pre-evaluation format is created, the investor should ideally freeze its design and attempt to validate it with historical records of internal and external cases. If this validation is conducted, an absolute threshold score can be defined to filter prospects more quickly.

3.1.5. Life sciences investor's package

An investor's package is a necessary and sufficient record generated by a company seeking sources of funding. This package allows potential investors to perform in-depth analyses of the technical, clinical, social and financial risks associated with that venture. In life science companies this package should be ideally comprised of the documents listed in Stage III of the Stage-gate investment model section, as shown in Fig. 2. Innovators and entrepreneurs in the life sciences industry should recognize the importance of this material for investors and should prioritize its completion before seeking private investment. Potential life sciences investors should also preemptively create required formats or an example investor's package to distribute among promising ventures that have not yet compiled this record to assist in the process.

3.1.6. Due diligence

The so-called due diligence stage is perhaps the most critical and time-consuming of all pre-investment activities in the life science investment process. The ultimate goal of this task is to transmit an accurate picture of the current state, as well as the future potential of the enterprise under evaluation. Many innovators and investors may perceive the due diligence process in life sciences as unnecessarily lengthy or scrutinizing; nonetheless, this activity ultimately ensures absolute clarity on the expectations from both investors and innovators and may constitute a useful preparation for regulatory submissions and other relevant hurdles that can determine success in private funding. Indeed, both investors and entrepreneurs can greatly benefit from thorough due diligence, especially when areas of improvement are outlined constructively. As with the rapid pre-evaluation tool presented previously, ongoing consultation with a life science advisory network becomes paramount to ensure complete understanding and accurate evaluations of investment prospects.

3.1.7. Negotiation of investment terms

Investment negotiation is usually conducted using term sheets, contracts, and other legal agreements. The negotiation process in life sciences investments is no different from other industries, and experienced investors are likely to be familiar with it. Based on our interviews, we suggest that these negotiations be conducted through a series of short formal meetings where both parties can revise together summaries of due diligence documents, as well as the involved parties and potential offerings. All sessions and negotiations should follow an agenda or antecedent unless otherwise specified. Both sides should acknowledge the importance of venture momentum and should target closing a deal as fast as possible or otherwise should agree to promptly refrain from continuing negotiations to focus on more compatible opportunities for both sides.

3.1.8. Evaluation and exit

Assessment of portfolio performance should be done periodically and according to the metrics defined in Stage I of our stage-gate investment model. These re-assessments can build upon previous ones to identify continuing risks and new obstacles and are a source of significant insight to both investors and entrepreneurs. These assessments should be done as frequently as possible to enable prompt corrective measures, but should never overburden the funded company whose highest priority should be to execute value-generation activities. Note that while there is a need for time and resource efficiency in all phases of the life science investment process, it is the exit time and conditions what truly defines investment profitability. From licensing agreements, Mergers & Acquisitions (M & A), to Initial Public Offerings (IPOs), the specific nature of these exit events is a critical point of discussion among entrepreneurs and investors to set clear expectations regarding timelines and profitability.

3.2. Case-control study

After eight months of observable implementation of the proposed model for life science investment process the trained company confirmed the execution of a $250,000 investment in early-stage life science venture developing a novel medical device. Before the end of the 12th-month study, an additional $100,000 follow-up amount was added to this venture totaling $350,000 (Fig. 1). Although the control firm confirmed an ongoing desire to execute a life science investment during the same period, no investment in this sector was completed. At the end of the study, both firms were approached to conduct a post-performance root cause analysis that could explain the observed differences in investment execution.

3.3. Post-performance root cause analysis (RCA)

Unstructured in-person interviews were carried out with the staff of both investigated investment firms to identify contributing factors and potential root causes that could explain the observed differences in investment execution of our single case – single control study. Anecdotal data surrounding investment decisions during the 12-month study period was collected in two independent sessions, one per evaluated firm. Interviewees were asked to name factors, situations, circumstances or conditions that contributed to the investment event or lack thereof. Relevant characteristics of the evaluated investment firms are included in Fig. 1. Information was analyzed to identify underlying process and potential root causes of the event. Several limiting factors were found to contribute to the lack of investment execution in the control firm compared to the case, these include: 1) Absence of standard operating procedures to quantitatively evaluate and compare life-science investment prospects; 2) Unfamiliarity with market trends, regulatory barriers and technical development timelines in the healthcare sector; 3) Excessive resources required to evaluate each investment opportunity; 4) Inaccurate estimations during valuation; and 5) Failure to efficiently compile accurate information regarding actual status of technical development, clinical validation and investment needs. These factors suggest that the availability of a life-science investment model may provide greater certainty to investors at the moment of considering investment opportunities. Notwithstanding these encouraging results, is

important to mention that a reduction in risk perception (as provided by the use of model) is not necessarily equivalent to risk reduction, which would require a more representative and lengthier study to prove. Although firm selection bias, unexpressed strategic focus, and organizational differences were identified as potential limitations in this root cause analysis, interviews did not reflect differences in these characteristics between the two evaluated investment firms.

4. Discussion

Every year, dozens of promising biomedical innovations gain significant media attention as research centers and private sponsors devote considerable resources to develop this field. Unfortunately, it is not unusual to see such developments being incubated for decades in academic settings through the use grants and other non-diluting funding (Chalmers et al., 2014). Despite the undeniable value that these sources of financing bring to life sciences ventures, they are ultimately unsustainable for most granting agencies, academic institutions and philanthropic organizations (Grazier and Metzler, 2016). The nature of these funding sources and their metrics of success often diverge from what is required for commercial success. For example, most sources of funding in academia are designed solely to optimize academic metrics and usually, fail to drive translation into market-ready products. A rare exception is the Coulter Foundation's Translational Partnership program, which has demonstrated that early stage investment in academic settings can lead to commercial success if managed correctly (Pienta, 2010). This suggests that private funds in the form of angel, seed, venture and corporate investments can be introduced earlier in the development process to enable more life science ventures to become valuable and sustainable businesses (Styhre, 2015). These activities; however, are only going to become attractive for the investment community when favorable conditions exist to profit from these innovations, and when useful tools to evaluate them are available to mitigate uncertainty and risk (Lehoux et al., 2016).

When new life science ventures do not meet investment goals, it is often attributable to lack of value proposition, clinical validity, or appropriate technical implementation, rather than to barriers imposed by regulatory agencies or reimbursement hurdles (Eisenberg, 1999). This suggests that a methodology capable of informing potential investors on how to evaluate key entrepreneurial dimensions in life sciences may reduce uncertainty and improve profitability of early-stage venture investment in a sustainable manner. To our knowledge, the presented stage-gate investment model constitutes one of the first attempts to formally understand this particular investment process, providing simple and intuitive guidelines to execute investments in life sciences. It must be noted that although many of the activities considered in this model are presented sequentially, they are likely to be conducted iteratively and potentially in a non-sequential manner. Also, when considering this model, the potential user must recognize some important assumptions and limitations present in this approach. For example, our model assumes that relevant life science investment stakeholders (e.g. entrepreneurs, regulators, investors, etc.) are aligned in their interest of bringing useful, safe, effective and affordable medical technologies to market as fast as possible (Eydelman et al., 2016; Robinson, 2015a, 2015b). Other potential limitation was the use of unstructured interviews to collect information and generate this model, did not allow for a quantitative justification regarding the relative importance of different stages and activities in each investment cycle. Despite this methodological limitation in the collection of qualitative data, the use of open questions allowed for the respondents to provide depth in their answers choosing their words, which helped us consider the investor's understanding and experience in this particular investment situation.

The inclusion of a small case-control study is only intended to demonstrate the feasibility of implementation in a single investment firm, yielding differences in investment execution when compared to a control. This provides a proof-of-concept in terms of model validation and definition as it complements the fact that only the decline in requests for change in the interview process was used as metric to validate model convergence in the initial phases of this study. Ensuring applicability of our proposed model to a wide range of investors is not necessarily justifiable through the present investigation and would require a larger-scale and more representative prospective study to be concluded. Further research in this respect should include: a larger number of interviewees, quantitative tools for information collection, additional metrics of model convergence, and long-term follow-up or more significant number of investment cases to measure investment profitability in a wider set of investment conditions avoiding potential selection bias.

Despite the many limitations of our case-control experiment, observable differences in investment execution and the results of a post-performance RCA are consistent with a reduction in risk perception in the trained firm using the presented life science investment model. In addition to the core stage-gate model, we have also presented for the first time a rapid pre-evaluation tool, which may constitute a valuable addition to the life sciences investor's toolkit. Care must be taken when using this tool as weighting and formatting were defined subjectively, sand could affect the validity of the obtained scores if not adapted to the specific strategic focus and investment thesis of the user. The availability of this simple pre-evaluation tool is a step forward in the realization of practical guidelines to assist life science investors; nonetheless, each user must judiciously examine it as not to acquire a false sense of certainty during screening. While scores can be obtained through pre-evaluation methodology, the use of these tools cannot provide absolute certainty on long-term profitability. We recommend that the oversimplifications of any pre-evaluation tool should be carefully reviewed, as to avoid unjustified execution or rejection of early stage investments due to unappropriated screening. Thus, our evaluation tool is only intended to complement the presented life-science investment model as an evidence-based framework to improve the yield of formally screened projects and reduce risk for life science investors.

5. Conclusion

Life-science innovation has seen an exponential increase during the last century, allowing tremendous social and economic change worldwide. Still, there is no scarcity of healthcare problems across populations, which not only has led to a higher demand for these products but also to unforeseen regulatory and funding barriers for its enabling technologies. Ensuring profitability of life science investments has been a topic of significant discussion over the years. In this sense, the advent of Biodesign-like training has indeed led to a higher volume of promising life sciences ventures, a situation that should (in theory) minimize risk for both innovators and investors alike. However, all previously reported life science processes and models are focus primarily on design and development activities and do not necessarily provide useful insight to the life science investment community. This gap negatively impacts the capacity of the wider investment community to profit from life science research development, validating the need for tools capable of improving the investor's capacity for informed decision making and risk mitigation in this sector. In this work, we have introduced such a tool in the form of a stage-gate investment process and a complementary rapid pre-evaluation format that could proof useful in the identification and management of promising life science investment opportunities. We encourage others to validate and refine the ideas presented here and to provide additional tools to democratize investment beyond the domain of niche healthcare investors, with the shared goal of supporting life science innovation and realizing their full potential for economic growth and social benefit.

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Appendix A. Supporting information

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