Science as Culture

ISSN: 0950-5431 (Print) 1470-1189 (Online) Journal homepage: http://www.tandfonline.com/loi/csac20

Valuations as Mediators Between Science and the Market: How Economic Assumptions Shape Pharmaceutical Trial Designs

Claes-Fredrik Helgesson & Francis Lee

To cite this article: Claes-Fredrik Helgesson & Francis Lee (2017) Valuations as Mediators Between Science and the Market: How Economic Assumptions Shape Pharmaceutical Trial Designs, Science as Culture, 26:4, 529-554, DOI: 10.1080/09505431.2017.1374940

To link to this article: https://doi.org/10.1080/09505431.2017.1374940

Published online: 17 Sep 2017.

Science as Culture, 2017
Vol. 26, No. 4, 529–554, https://doi.org/10.1080/09505431.2017.1374940

Valuations as Mediators Between Science and the Market: How Economic Assumptions Shape Pharmaceutical Trial Designs

CLAES-FREDRIK HELGESSON * & FRANCIS LEE **

*Department of Thematic Studies—Technology and Social Change, Linköping University, Linköping, Sweden, **Department of History of Science and Ideas, Uppsala University, Uppsala, Sweden

How can economic assumptions be present in the heart of commercially driven drug development research? Such assumptions underpin industry-based bio-statistical discussions around a new pharmaceutical trial design, the 'compound finder'. This example illustrates several ways in which trials might be designed and situated in the larger setting of interlinked valuation practices central to the development, distribution, and use of pharmaceuticals. It shows how economic assumptions and considerations can be differently entwined with endeavors to produce knowledge. Different trial designs may further differ in what knowledge they produce. Adaptive design trials (ADTs), of which the compound finder is one kind, share the feature that they might be the object of thousands of simulations to specify the design taking many different kinds of considerations into account. These considerations include several economic aspects such as trial costs and assumptions about the future market. ADTs will likely continue to become more common in the years to come, even if the future for the specific compound finder trial design is uncertain. Yet, the continued rise in importance of ADTs means a further intimate entwining of economic assumptions into the specification of trial designs. This will be consequential for what knowledge is produced as well as where and how treatments are assessed.

KEYWORDS: drug development, economic assumptions, trial design, medical research, valuation

Correspondence Address: Claes-Fredrik Helgesson, Department of Thematic Studies—Technology and Social Change, Linköping University, 581 83, Linköping, Sweden. Email: claes-fredrik.helgesson@liu.se

Introduction

The availability of effective pharmaceuticals is central for the provision of good health care. Many things contribute to determining what drugs are available for treating patients with certain conditions. These include the many nooks and crannies of how healthcare is provided, such as the organization of health services where you live, what guidelines govern the prescriptions of physicians, and so on. Other matters determining the availability of treatments relates to how the development and approval of drugs are organized. Pharmaceuticals need to have regulatory market approval to become available for patients and their physicians, and such regulatory approval requires sufficient amount of research and clinical trials. As a consequence, decisions made in the research stages of drug development are consequential for what drugs will eventually become available to patients.

We are, in this paper, broadly speaking interested in exploring how the economic is entwined in shaping scientific endeavors. The paper specifically examines how economic assumptions shape decisions in the heart of commercially driven drug development research. We focus in particular on how economic assumptions about the downstream market can be made present to shape commercially funded research to develop drugs. In other words, the paper examines how economic assumptions shape drug development, and consequently what pharmaceuticals may become available on the market.

The case we study in this paper is an industry-based bio-statistical discussion around a specific pharmaceutical trial design called the 'compound finder'. This case highlights how ideas about markets for pharmaceuticals can be folded onto ideas about how to design trials and how to select candidates to introduce in said markets. The discussion around the compound finder is interesting because it provides glimpses into the deliberations when choosing drugs to develop and introduce on the market. This specific trial design has been suggested as a tool for choosing what drug candidate to further develop out of a portfolio of candidates. In brief, this trial design is conceived to simultaneously test several drug candidates and to identify a single drug candidate to bring forward for further trials and subsequent market approval. Hence, it is proposed as a device for a pharmaceutical company when determining what drug it will eventually make available for patients within the therapeutic area.

Our examination centers on the specific construction of the compound finder trial design and how it is contrasted with other possible arrangements for developing and selecting drugs to introduce on the market. The overall guiding question for our examination is: What does the discussion about the compound finder trial design illuminate as regards how economic considerations and assumptions are entwined (or not) with endeavors to produce knowledge? We further ask what different valuations are implied in the discussion around the compound finder and other alternative trial designs?

Our conceptual starting point is that 'the economic' and 'the scientific' do not constitute separate spheres of practice that are only linked by the successful 'translation' of scientific activity into market practices. With an approach informed by the social study of markets (e.g. Callon *et al*., 2007) and science and technology studies (STS), we instead understand drug development as involving a series of valuations that each might entail a variety of 'scientific' and 'economic' aspects.[1] This focus on multifaceted valuations enables us to examine how assessments of drugs can vary in their setup and localization. Taking a pragmatist approach to valuations, we further posit that the configuration and interlinking of valuations are consequential (see, e.g. Helgesson and Muniesa, 2013). This focus on the setup and localization of valuations thus provides a gateway for examining how economic assumptions and considerations can appear as an integral part in the knowledge production of drug development.

Conceptualizing Links Between Research, Development, and Market

What are the possible relationships between endeavors within research and development and those taking place within markets? This paper touches on broad and prevailing research themes and questions. These include, first, the large and fragmented bodies of work centered on the possible relations between scientific research, product development, and markets. These discussions further include work about how scientific and economic practices might influence one another. A second research theme is that of the role of market representations and the performativity of economic theory in shaping market practice (see, for instance, Callon, 1998a; Kjellberg and Helgesson, 2007; MacKenzie *et al*., 2007; MacKenzie, 2009). We touch on some central points about these two themes in this section. Thereafter, we present a conceptual framework developed to explore how economic assumptions are entwined with scientific endeavors in terms of the configuration of valuation practices.

The often invoked 'linear model' of innovation suggests that basic research precedes applied research, which in turn precedes effects in the economy. This *model of innovation* is as often criticized as it is cherished or implied in policy measures (for a development history, see Godin, 2006; on the performance of temporal and organizational purity in the sciences, see Lee, 2015). One deficiency, among several, of the linear model is that it presumes the activities of basic research, development, and so on to be well delineated from one another. This implies understanding innovation as entering and shaping a broader social and economic reality only at the end of such a linear trajectory. Much work in STS can be seen as criticizing such understandings of science and technology. Concepts like 'the social construction of technology', 'actor-network theory', and 'the mangle of practice' (Callon, 1986; Bijker and Pinch, 1987; Latour, 1987; Pickering, 1995) highlight how science and development practices at every instance are embedded or entwined with the social.

In STS, the economic is often characterized as part of 'the social' while rarely given much dedicated attention. One important classic exception to this neglect is contained in the notion of *techno-economic networks* suggested by Callon (1991), which exemplifies a focused effort within STS to examine the many interactions between science, technology, and the economy. This notion portrays activities related to innovation as linking a multitude of actors and intermediaries where there are no pure 'economic' or 'social' spheres isolated from scientific practice and technological development. The techno-economic network is defined as 'a coordinated set of heterogeneous actors which interact more or less successfully to develop, produce, distribute and diffuse methods for generating goods and services' (Callon, 1991, p. 133). The role of *intermediaries* is a central point in this conceptual model indicating a variety of elements that circulate among the heterogonous actors of the network (Callon, 1991, p. 135). The notion of techno-economic networks further involves the notion of *configurations*, which signifies the different ways in which relations of translations between elements might be ordered (Callon, 1991, p. 146). This broad conceptualization opens the possibility of investigating more complex links and folds between what Callon heuristically simplified as the *scientific*, *technical* and *market poles* (1991, pp. 133–134).

The emergence of STS-related studies of markets (Callon, 1998b; Callon *et al*., 2007), and most notably studies of financial markets (MacKenzie and Millo, 2003; MacKenzie, 2006), marked a broader move within STS to take the economic and markets more seriously. The notions of performativity and market devices are the most prominent expressions of this move. They have to a large extent focused on how knowledge about markets, encompassed in say models from economics, can shape markets. Yet, contrary to Callon's work on techno-economic networks, this more recent attention to markets in STS has been associated with shifting attention away from what shapes science and technology.

A paper by Miller and O'Leary (2007) comes close to looking at the complex interplays between technological development and the shaping of markets. The paper examines how 'Moore's law' within the IT industry links technological development and markets. The law predicts a doubling of electronic elements on a semiconductor every two years without a corresponding increase in cost. Miller and O'Leary see 'Moore's law' as something that actors in related markets use to make investment decisions. With reference to Callon's work on techno-economic networks, they see 'Moore's law' as a *mediating instrument* that links science and the economy, or, to use Callon's (1991) terms, as something that links the science and market poles.

One analytical advantage with the notions of heterogeneous actors, mediating instruments, and configurations is that they are not conceptually or intuitively linked to a specific pole such as the market pole or science pole. This is why they are useful for examining the many ways practices around the different poles might be interlinked. We would, in this context, like to suggest that the notion of *valuation as a social practice* (see, e.g. Muniesa, 2012; Helgesson

and Muniesa, 2013) has a similarly useful quality in this context. Taking valuation to signify any practice where the value or values of something is negotiated and established, means that 'valuations have many objects as well as many subjects, and is a process that takes many forms' (Helgesson and Muniesa, 2013, p. 4).

A central tenet in the emerging field of valuation studies (for an overview, see Lamont, 2012) is that the setting, procedures, and devices involved in these practices influence their outcome (see, for instance, Fourcade, 2011; Zuiderent-Jerak and van Egmond, 2015). The specific setup of how to assess who should be allocated an organ for transplantation, to take one striking example, not only influences how that allocation work is done, but determines what values are seen as central and which recipient will get an organ (Roscoe, 2015). Taking a cue from the notion of techno-economic networks, attention to valuation practices warrants looking at how valuation practices are *configured.* Examining the configuration of a valuation, then implies examining the involved actors, devices, metrics, and procedures as well as how their relations are ordered. We suggest that examining the configuration of valuation practices is a useful tactic for examining the complex links between the scientific, technical, and market poles. In relation to this paper's guiding question, this means being attentive to how economic assumptions are present in valuation practices around the science pole.

This broad conceptualization of valuation suggests that there are many valuation practices involved in any techno-economic network. In the realm of drug development, these would include the valuations done when deciding which compounds to develop. It involves the valuations of molecules in large-scale biomedical mapping (Lee, 2015). It involves the valuations done to specify the research design of specific trials (see, e.g. Helgesson *et al.*, 2016) and when choosing what design to specify in the first place. It includes the regulatory valuations done when assessing whether a particular drug should be granted market approval or not (see, for instance, Abraham and Davis, 2007). Valuations are subsequently furthermore done when pricing drugs and when assessing their usefulness in the health care system, through health technology assessments, guideline development, and so on (see, e.g. Sjögren, 2006; Sjögren and Helgesson, 2007; Moreira, 2012; Rabeharisoa and Doganova, 2016).

We frame our exploration of how the economic is entwined with scientific endeavors in terms of how valuations are configured. We are furthermore interested in how different valuations may be folded or interlinked with one another (cf. Helgesson, 2016). In what ways, for instance, might the valuations done when conducting a drug trial impinge on the subsequent assessment of a drug's usefulness in the health care system? Or, conversely, how might an economic assumption about the 'downstream market' be made part of the valuations that first favor and then specify a trial? With inspiration from the notion of mediating instruments (Miller and O'Leary, 2007), we take the foldings of valuations as a way to identify the *mediating roles of valuation practices*. This invites us to examine how the compound finder trial design is conceived as part of a broader

configuration of different valuations and how economic assumptions are made part of the valuations that shape trial design.

Seeing a scientific endeavor such as trial design as situated in a setting of interlinked valuation practices provides a distinct vantage point for examining what shapes knowledge production. This vantage point is agnostic about what can be brought to bear on the endeavor. It allows therefore us to be attentive to the variety of considerations and economic assumptions that are mobilized, be it concerns about experimental ethics, costs, or indeed expectations of future profits. As such, it becomes a vantage point for empirically examining how economic models, forecasts, and expectations might shape scientific knowledge production. Hence, this proposed framework allows for examining the entwining of economic considerations and assumptions with scientific endeavors that are less linear than a framework only drawing on the performativity program.

Traditional Trials and the Emergence of Adaptive Design Trials

On the Empirical Material

This paper is part of a larger study about the valuations performed in trial design. The sub-study on adaptive design trials (ADT) draws on interviews with bio-statisticians (in industry and at the European Medicines Agency (EMA) and FDA), scholarly articles and other documents, and participant observation at workshops and online lectures. The total corpus comprises roughly 100 journal articles and book chapters, government documents, slide presentations, transcripts of five interviews, and field notes. These materials have been organized and coded using a software for coding and retrieval. This paper obviously only uses a small sub-set of these materials. Yet, our identification and analysis of the specific case are informed by our broader examination of the valuations performed in the designing of ADTs.

Randomized Controlled Trials in Drug Development and Market Approval

Since the 1960s, the randomized controlled trial (RCT) emerged as the prime form of experimental design for the development and testing of new drugs (Marks, 1997; Fisher, 1999). The primary design features of the RCT are that it includes a *randomization* where a treatment, or placebo, is randomly distributed within a group of recruited patients, the trial subjects. The creation of sub-groups is to provide a *control* to the treatment being tested, for instance, by giving one group a placebo. The sub-groups, or *trial arms* to use the vernacular of trials, are to be similar in all aspects but for the treatment they receive. According to the ideal, the allocation of treatment to individual trial subjects should be double-blind. The intention behind the double blindness is that neither trial subjects nor staff seeing the patients knows who gets what treatment. The statistical

analysis of the data is performed after the conclusion of the trial. It is only in that moment that the treatment outcomes for each enrolled patient are paired to the hitherto concealed information about what treatment (or placebo) he or she had received.

Clinical trials within drug development are classified in terms of phases in relation to a possible market entry (phases I–IV). Trials up to phase III must be done before a drug can be approved, and it is regularly required to have a few successful phase III trials to gain marketing approval by agencies such as the USA's FDA. The RCT has become a regulatory 'gold standard' method for producing the results needed for market approval. The RCT is in this respect not only a dominant trial design in drug development, but also in the regulatory context (see, for instance, Will and Moreira, 2010).

The linear sequence of trials implied in the categorization of phases does not mean that market and regulatory considerations are irrelevant in the earlier stages of drug development. Companies compete, for instance, during development to have their drugs on the market as early as possible. Consequently, trial designs are regularly discussed in terms of how they contribute to reducing the 'time to market'. There might be instances where a phase II trial is designed to compare the drug in development with a competitor's already approved drug and hence making the trial precede future competition in the market. Moreover, the phases of trials in drug development now affect 'the disclosure of information used in pharmaceutical company valuations' (Carpenter, 2010, p. 294). The disclosure of the success or failure of a trial can have effects on stock prices of pharmaceutical companies. Trial design in commercial drug development is thus always in a context where there are pertinent market, regulatory, and financial considerations to be made. The market pole is hence present in the science pole (cf. Callon, 1991) as economic assumptions about subsequent regulatory and market conditions.

Scholars have examined how economic considerations and assumptions might influence the regulatory assessment of drugs and, as a consequence, the design of the trials leading up to the application for market approval. Abraham and Davis (2007), for instance, compared the regulatory treatment of two non-steroidal anti-inflammatory drugs in the US and UK. According to these authors, the UK regulator was more influenced by industry expectations and approved these two drugs, only to then withdraw them later on safety grounds. In the US, the FDA never approved them. Hence, the UK regulator put a greater emphasis on making the drugs available than did their US counterpart.

The balancing of the regulatory assessment of a new drug's efficacy, safety, and the benefits of early access is also discussed by others (e.g. Eichler *et al*., 2008; Shea *et al*., 2013). The balancing of such concerns can, as is indicated by a study of FDA oncology drug approvals (Shea *et al*., 2013), be reflected in the acceptance of studies focusing on less demanding proofs of efficacy (so-called surrogate endpoints). Such regulatory orientations towards faster approval directly

influence the design of the phase III trials necessary for the market approval application. Hence, several studies show how economic considerations and assumptions are at play in the nexus between drug development and trial design on one hand and regulatory approval on the other.

Adaptive Design Trials

The gradual development of ADTs in the last two decades is tied to efforts to increase the efficiency and speed of drug development. There have been several efforts by regulators, bio-statisticians, and industry associations to develop and analyze the properties of various forms of ADTs (Food and Drug Administration, 2006; European Medicines Agency, 2007; Chuang-Stein and Beltangady, 2010; European Medicines Agency and EFPIA, 2010; Food and Drug Administration, 2010; Tufts CSDD, 2013). A common trope in these discussions is how ADTs allow for more efficient and swifter ways to reach the market in the face of strong competition. For example, an overview article on adaptive design for early-phase trials, stressed that 'adaptive designs allow more efficient use of information for decision-making, which ultimately translates into improved probability of success and *shorter overall time to market* for successful products' (emphasis added, Marchenko *et al*., 2014, 28).

One 2013 estimate suggested that simple adaptive designs were used in 20% of clinical trials across the industry (Tufts CSDD, 2013, p. 2). Although the emphasis was originally on developing ADTs for phase I and phase II trials, they are now increasingly also used for phase III trials. A survey of industry seeking advice on ADTs from the European regulatory agency EMA highlighted that a majority of these concerned confirmatory phase III trials and that a majority of these were accepted or partially accepted (Elsäßer *et al*., 2014). In the US, the 21st Century Cures Act was passed into law in late 2016, which tasked FDA to update their guidance for using results from ADTs when approving drugs.[2]

The notion of 'adaptive' points to the distinctive feature of ADTs. Contrary to traditional RCTs, they include the possibility of changing aspects of the trial while still in progress. These possible changes are to be planned before the trial begins, but are to be triggered by certain outcomes of the trial whilst still running. The so-called interim analysis of data during the trial, and the possibility to make changes based on such analyses, are the two interlinked features that are strikingly different from traditional RCTs.[3] Other important features of RCTs, such as randomization, control groups, and double-blind process, are still central in ADTs. The specific features of ADTs might appear as primarily technical. Yet, they also have consequences, as we will show, for the valuations that specify a trial design and how economic assumptions can become part of these valuations.

A mid-trial change in the probability with which additionally recruited patients receive a certain treatment would be one example of a pre-planned change in an ADT. Such a setup could have an initial group of recruited patients randomized

evenly between five different doses. Subsequently, more patients are randomized to the doses that appear to provide the most promising results. It involves an adaptive algorithm comprising pre-planned rules for adaptations that decide how the trial should change based on what emerges in the repeated data analyses. As we will show, the possibility to plan such seemingly innocuous changes has momentous consequences for trial specification and, ultimately, for what knowledge is produced.

All experimental designs can be seen as both the outcome of valuations and as devices for performing valuations (cf. Helgesson *et al*., 2016). The valuations involved when specifying an ADT become more sophisticated than traditionally because an ADT provides a broader range of specific design options. ADTs are furthermore interesting since the adaptive algorithm can be specified to perform more sophisticated valuations of treatments. Hence, ADTs are more malleable than traditional RCTs and this makes the valuations shaping their specification, and the valuations they subsequently can perform, more sophisticated. A genealogical analysis of the emergence of ADTs shows how these new forms of trials shift to a 'moral economy of anticipation' in medical research (Montgomery, 2017).

ADTs are often tied to a context with strong competition to reach the market and desires to speed up drug development. Their more elaborate design, involving more elaborate valuations, makes it possible to tailor trials that when executed are likely to evolve and focus on matters that are considered interesting. These qualities of ADTs make them a compelling site when taking an interest in how economic assumptions and considerations can become part of the valuations that select and specify a trial design. Hence, it points our interest to what valuations are made when choosing and specifying a trial and what valuations such a trial itself performs. We will now turn to the discussion around the compound finder trial where the trial is used to incorporate what the designers call 'a competition' between compounds into the trial algorithm.

The Case of the Compound Finder Trial

A Trial Where Several Compounds 'Compete' for the Same Indication

> The Fairmont Hotel, Washington, February 2015. I'm at this posh hotel to attend the ISCTM meeting (*The international Society for CNS Clinical Trials and Methodology*). The meeting is in a ballroom downstairs of the kind you find at many large American hotels. I'm here not so much to listen to the speakers, but to meet someone from FDA during a break. Yet, I quickly realize that the session is very interesting. It is titled *Adaptive Design in The Real World: Implications for Neuroscience Clinical Studies*. Vladimir Dragalin, a Vice President at Janssen Pharmaceuticals, opens the session with a presentation to give an *Overview of Adaptive Design*

> *Methodology*. In his talk, he mentions the 'compound finder' as a form of adaptive design trial useful when you have several compounds in the same firm because of a merger and want to find which one to proceed with. (Adapted from field notes, 18 February 2015)

The compound finder is one kind of ADT that is suggested could be conducted at the so-called 'portfolio level' of a pharmaceutical company. The portfolio level means a trial above the development program level of an individual compound. In a compound finder trial, several compounds are included in a single trial with the aim to identify which of these to move forward for further development. The compound finder is hence envisioned as a phase II trial to precede phase III trials or indeed a trial that can be extended to become a so-called seamless phase II/III that in a second stage generates results for a market approval application.

The compound finder trial design has been described by Michael Krams and Vladimir Dragalin (both at Jansen) in a book chapter as well as in presentations such as the one described above. They sometimes refer to this trial as staging 'a competition' between different compounds: 'The competing options are three different compounds for the same indication. The adaptive design aims to identify the compound with the most impressive therapeutic index to pursue in the further' (Krams and Dragalin, 2014, p. 72). In the chapter, they present a conceptual case study in the area of Alzheimer's disease. Their case study compares a conventional setup with three RCTs each investigating one compound, with a compound finder trial that simultaneously investigates the three compounds within a single trial:

> [The] conventional development strategy [with three trials] is compared and contrasted with an adaptive compound finder proof-of-concept study design that investigates several compounds in a single trial. The objective is to find with high probability the 'best' compound using adaptive allocation of subjects to competing treatments. (Krams and Dragalin, 2014, pp. 72–73)

The basic setup of this compound finder trial is to have an initial batch of patients randomly assigned to one of the three different competing compounds or to placebo. In the trialist vernacular, the trial has four 'arms'—one placebo and one each for the three compounds.[4] Subsequently recruited patients are to be randomly assigned to the different arms according to an algorithm that favors the compounds that, according to the interim analyses, appear to be more promising during the trial. The trial continues in several steps of interim analyses, which lead to further alterations of the randomization. In the later stages of the trial—through the gradual elimination of compounds—new patients are randomized between the single remaining compound and placebo before the trial is concluded and the final analysis is made.

The adaptive algorithm makes the trial gradually focus more and more of the attention on the compound that emerges as most promising. The implication of this setup is that a compound needs to bring out promising outcomes in the early stages of the trial to become fully investigated. With the notion of 'competition' sometimes used around the compound finder, one might think of it as a form of tournament-like competition between the compounds. From the perspective of valuations, the compound finder is a sophisticated valuation machine inside a pharmaceutical company tasked to assess several compounds at once. The designing of such a trial qua valuation machine entails complex valuations (cf. Helgesson *et al*., 2016). The valuations that go into selecting and specifying the trial design are decidedly at the science pole, but can simultaneously involve economic assumptions about the market pole within the techno-economic network (cf. Callon, 1991).

The point of the case-study exercise presented by Krams and Dragalin is to investigate how a compound finder trial compares to a more conventional strategy involving a sequence of three trials, where each test one of the compounds against placebo. The two development strategies compared were graphically summarized on a slide presented by Dragalin at a KOL lecture (see Figure 1).

The rationale for the compound finder given in the slide above is to 'find with high probability the "best" compound'. The comparison Krams and Dragalin presented in the chapter was based on numerous simulations running through different *scenarios.* In these simulations, Krams and Dragalin further compared how well a conventional design with three trials would perform with an adaptive design compound finder design (the two sides in Figure 1). The key question in the case-study exercise is how well these two different development strategies work in different scenarios. However, before looking at their comparison of different development strategies, we need to examine how this exercise was motivated.

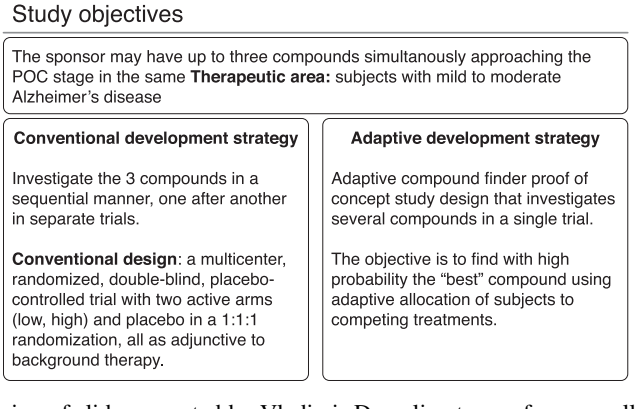

Figure 1. Redrawing of slide presented by Vladimir Dragalin at a conference call KOL lecture 10 April 2015 in the KOL lecture series on adaptive designs organized by a network of bio-statisticians interested in adaptive designs.

From a Competition on the Market to a Tournament-Like Competition Within a Trial

There are several arguments why it is useful to deploy a compound finder trial. The book chapter by Krams and Dragalin opens by relaying the large failure rate of phase III trials and that ADTs might remedy this. Their idea is that such a trial can improve decision-making regarding what to move forward to subsequent development stages. In their words, 'an adaptive design strategy at the portfolio level can increase the value of the pipeline by maximizing the probability of success and reducing the cost of development' (Krams and Dragalin, 2014, p. 71).

Krams and Dragalin present the compound finder as a tool for a pharmaceutical company to use when deciding what compound to bring forward to the costlier phases of drug development. The framing of this as a decision problem of investing in the right compound is further elaborated in an oral presentation. In the above-mentioned session in Washington, Vladimir Dragalin noted how a compound finder strategy can be useful when you have several compounds in the same company as a *result of a merger*. Hence, the problem of selecting compounds for further development is tied to how such portfolios of compounds have been created by a merger. A person involved in developing the case further elaborated this post-merger rationale for using a compound finder design:

> [*Y*]*ou don't want to compete with yourself.* . . . If one company is buying the other company, or they merge, usually they have in their portfolio different compounds; and *the whole reason of merging is to reduce the competition.* You don't want to develop two drugs all the same, let's say in schizophrenia. This is why the strategy I describe is appealing. (Interview with NN, July 2015)

This image of a post-merger situation gives another facet to the notion of 'competing treatments'. The post-merger scenario introduces competition between treatments as something to be avoided in the market. Consequently, the argument goes, the post-merger company should avoid developing several drugs that would subsequently compete with one another on the market. Here they are thus evoking a particular company view about competition between treatments in the market, and how such a competition can be avoided by instead devising a tournament-like competition within the trial. The tournament-like competition between treatments within a compound finder ADT is to take the place of a competition between approved drugs on the market.

Introducing a post-merger situation thus hints at alternative circumstances more implicitly 'compared and contrasted' with the adaptive design compound finder development strategy. Their case-study exercise primarily compares the compound finder development strategy with a conventional development strategy using three consecutive trials for finding the compound to move forward. The

post-merger situation suggests an alternative pre-merger market situation where several independent firms each develop drugs to compete on the market, or indeed the alternative where a post-merger firm develops and introduces several compounds to compete with one another on the market. These two implicit alternatives are seen as inferior to any development strategy where there is a setup to select a single compound to introduce on the market. In sum, a tournament-like competition between treatments inside a post-merger firm is seen as preferable to a competition between treatments on the market.

The assumption that it is unfavorable for the company to introduce competing treatments into the market is clearly central in the valuations that shape this development strategy and the selection of the trial design. Conceptually, this is an example of how a market representation (cf. Kjellberg and Helgesson, 2007) is brought into these valuations within drug development and makes these valuations mediate between the science and market poles (cf. Callon, 1991; Miller and O'Leary, 2007). Hence, the compound finder trial is shaped taking assumptions about markets into account as well economic assumptions about what provides the more favorable company position within said markets.

Specifying the 'Valuation Machine'

The challenge facing Krams and Dragalin was to find a way to test whether the development strategy involving the compound finder trial is better than the alternative. They needed to test if the compound finder valuation machine simultaneously investigating three compounds is better than a sequence of three traditional RCTs each testing one compound. They did this comparison through numerous computer simulations testing each design in a variety of different scenarios.

Each scenario in the testing represented a different possible distribution of efficacies for the different compounds since the actual efficacies of the compounds cannot be assumed to be known before the trial has been run. The formulation of scenarios creates several different possible qualities of the portfolio. Hence, one scenario stipulated that none of the compounds were effective. Other scenarios stipulated situations where combinations of one or several of the compounds were significantly or moderately effective. A simulation then tested how well a particular specification of the compound finder trial or the set of traditional RCTs would perform in a given scenario. Hence, the scenarios were different assumed possible realities, and the simulations tested how well the different designs and setups would produce relevant knowledge and identify promising compounds given each scenario.

Of interest in the simulations was how different trial designs perform in different scenarios where performance largely was assessed in terms of ability to produce useful knowledge and save resources. The questions asked of the simulations were: How good is this design in identifying an effective compound in scenarios where such a compound is to be found? How good is this design to

declare a failure to find a good compound in scenarios where there is no working compound to be found? The comparison of the development strategies looked at several operating characteristics: 'the average number of subjects, the average study duration, and probability of correctly identifying the "best" compound' (Krams and Dragalin, 2014, p. 73). The simulations thus became a way to produce data for assessing a specified trial as a valuation machine, and as a consequence, to make it possible to compare the performance of the two development strategies.

The final comparison of the two development strategies—the three traditional RCTs or the compound finder—required them to be fully specified, for example, the pace of patient recruitment and number of interim analyses. Therefore, the comparison in the chapter had been preceded by the crucial work to fully specify important design aspects for each trial. The chapter is, however, sparse with information about the testing and tweaking of parameters done before arriving at the final specified trials within the two development strategies. To examine these valuations, we will first look at a few trial parameters as presented in the chapter and then see what an interview with one of those involved can provide regarding the work to specify them.

The specification of trial parameters is crucial since the parameters determine how a trial will respond to different conditions (scenarios). This is especially true for the specification of the adaptive algorithm that forms the core of an ADT such as the compound finder. Among the many parameters set for the simulation algorithms of the compound finder are how many patients to be initially recruited for the first randomization to each trial arm, the allocation rule (who gets what), and the definition of stopping rules for when to stop the trial declaring it a success or a failure. Such parameters can be considered multivalent where each has financial, ethical, and epistemic consequences.[5] As our informant stressed, they are difficult to specify since their specification can have several consequences for how the trial performs. Simulations played a pivotal role in setting the parameters so that the compound finder would perform well when confronted with different scenarios. The compound finder design was tweaked to perform well in the subsequent comparison with the RCT:

> These are controlled parameters of the design and we run a lot of other simulations in background to find you those vectors. That was a laborious task for me because I got a very bad performance with some values of those parameters, worse than the conventional [strategy]. I was trying to play with them through repeated simulations until I found a performance which was good. (Adapted from interview with NN, July 2015)

What our informant told us was that the tweaking of parameters was laborious. It was particularly challenging since several parameters might influence the same

operating characteristic. The work consequently involved running numerous simulations for each scenario to find a good value for one parameter and then moving on to the next one. Yet, a subsequent changing of another parameter might modify what is a good value for a previously set parameter. Our informant therefore emphasized that such exercises cannot be done with the ambition of finding optimal values for all parameters, but to find a set of parameters that makes the compound finder largely beat the conventional development strategy:

> *Usually we reduce our ambition from finding the optimal to beating the convention.* So that is the approach. I'm trying to build an adaptive option which will be better than your conventional design strategy. Maybe I will not be able to find an adaptive option which will beat you across all scenarios, but then it will be a judgement for you. If I build an adaptive design which beats your conventional design strategy, let's say for eighty percent of the possible scenarios, then you can say: 'OK, I'm satisfied!' (Adapted from interview with NN, July 2015)

The final comparison between the two strategies was hence preceded by a large amount of work to test and finally settle all trial parameters. The comparison presented in the book chapter compares these two development strategies across numerous operating characteristics. These operating characteristics had been estimated for each scenario-design combination by 1,000 simulated trials. This, then, is what provided the material for assessing how the two development strategies compared across the different scenarios. The comparisons involved, for instance, the probability of stopping early in a scenario when none of the treatments are effective ('flat scenario'), and in scenarios where one, two, or all treatments are moderately or highly effective. One scenario, for instance, assumed that all treatments were highly effective (The 'equal 4pts scenario'). This quote gives some flavor of the comparing and contrasting of the two strategies:

> Under 'flat' scenario, the adaptive design [compound finder] is a clear winner, requiring on average 370.75 subjects and the average study duration of 176 weeks. The conventional strategy requires an additional 178 subjects and prolongs the study duration by 155 weeks. Under 'equal 4pts' scenario, the situation is reversed because the conventional strategy stops with high probability (0.998) after the first trial. (Krams and Dragalin, 2014, pp. 85–86)

The adaptive design compound finder did not emerge as the best valuation machine for all scenarios. It performed less well in the scenario where all compounds were effective. Here, the sequence of three RCTs would with high probability find a good compound already in the first trial and hence preclude the two other planned RCTs from proceeding. Yet, overall, in the simulations the compound finder was considered as having better operating characteristics. The

compound finder was shown to have a high probability of finding an effective treatment in scenarios where a good treatment was to be found. It was, furthermore, shown, on average, to involve fewer trial subjects and have a shorter total duration.

In addition, the adaptive design compound finder was further held up as having the additional advantage of providing 'a competition' between all treatments where they all initially had a chance of being 'fully' investigated (Krams and Dragalin, 2014, p. 88). The adaptive algorithm of the compound finder performed the role of a selection mechanism that a priori handles all treatments the same, but gradually disfavors treatment(s) that have a low probability of 'beating' placebo. This differs from the conventional strategy with three RCTs since this strategy might result in a promising treatment not being investigated at all if another treatment appears promising in an earlier trial in the planned sequence. In contrast, the compound finder trial with its adaptive allocation rule provides an initially equal tournament-like competition between all considered treatments.

*

We could not find evidence that a compound finder trial has ever been run with real patients. Probably it has thus far only been run thousands of times on a massive number of virtual patients to produce the above-discussed case study. Nevertheless, the surrounding discussion illustrates important aspects of ADTs as a new mode of knowledge production. This concerns not the least the importance of complex valuations involving simulations to pre-specify how the epistemic attention is to be directed. Back to the beige ballroom at the Fairmont Hotel in Washington that freezing day in February 2015:

> Towards the end of his presentation, Vladimir Dragalin raises some cautionary remarks regarding adaptive design methodology. He stresses that adaptive designs will not make drugs work, and that they are not a panacea for everything. *They can only, he affirms, redirect attention.* (Excerpt from field notes, 18 February 2015)

Discussion

The Many Arrangements for the Drug Development Process

The compound finder trial provides a suggestive re-ordering of what would take place where and when in the development of new treatments. It is for its proponents compelling to have a single trial stage as a tournament-like competition between treatments. This arrangement takes the place of other arrangements where several drugs are developed in parallel to subsequently compete on the market. It further takes the place of a development strategy using several consecutive trials for selecting a single candidate to move forward.

Instead of these alternative arrangements, the compound finder provides a valuation machine that facilitates 'choosing which development candidate to back when there is a large portfolio of products competing for a fixed level of investment' (Krams and Dragalin, 2014, p. 70). The compound finder is a product of a valuation that mediates between the science and market poles (cf. Callon 1991; Miller and O'Leary, 2007), and becomes in itself a valuation and selection device configured to attune to a particular assumption about what subsequently will provide the more favorable company future market position.

The compound finder trial can conceptually be framed as part of a larger particular configuration of interlinked valuation practices (e.g. Helgesson and Muniesa, 2013; Helgesson, 2016). These include the valuations involved when designing the trial (using simulations), the valuations performed by the compound trial itself, and the projected future assessment of regulatory agencies of an application for market approval of the single 'winning' compound after possible further phase III trials.

The discussion further indicated alternative arrangements, such as the traditional development strategy involving sequential RCTs or the pre-merger situation with several independent firms each developing drugs to compete on the market. Each such indicated arrangement similarly can be understood as involving a particular configuration of interlinked valuations. We will in this section analyze the different configurations of interlinked valuations implied in the discussion around the compound finder and other alternative designs. Of particular interest is how the valuations in these configurations mediate between the science and market poles.

Figure 2 summarizes the different arrangements indicated in the case story. Our depiction presents the various ways the development programs of compounds are located in one or more firms, and whether 'a competition' is located within a trial or between drugs on the market. Arrangements 3 and 4 represent the two development strategies at the center of the case discussion. There were, in addition two other arrangements implied in the case discussion: arrangement 1 here represents the pre-merger situation with two separate firms each developing a drug for the same medical condition, and arrangement 2 represents the strategy of one firm developing two drugs in parallel to the effect of subsequently 'competing with oneself'.

Each different arrangement has specific features. This includes how and where it is decided what drugs are available for treating patients of a certain condition. Arrangements 1 and 2 provide more than one drug to the market. Arrangements 3 and 4 are characterized by a pre-market selection of what subsequently will become available on the market. We will in the following two sections first examine how valuations are configured and interlinked in the different arrangements and second examine what the different configurations imply for the knowledge produced.

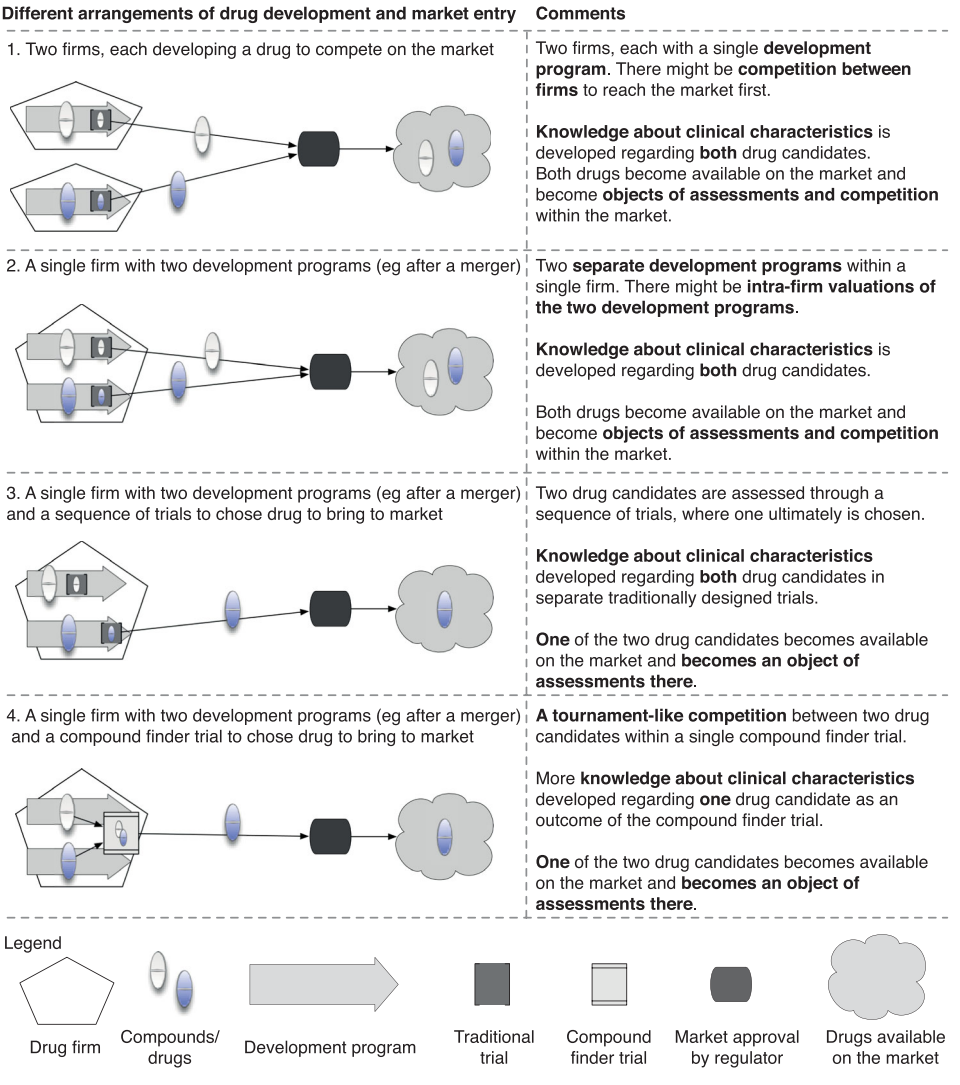

Figure 2. Different arrangements of drug development and market entry indicated in the case story about the compound finder trial. Possible further necessary phase III trials are omitted in this schematic diagram since they would be the same in all four arrangements.

The Many Differently Configured and Interlinked Valuations

The most conspicuous difference in the arrangements indicated is the varying placements of 'competition'. This points to the more general differences as to where the different drugs, or indeed drug candidates, are set against one another as objects of assessment for making selections. In arrangements 1 and 2, the drugs are seen as competing and being assessed on the market as approved drugs. In arrangements 3 and 4, they are instead essentially objects of assessment within

a single pharmaceutical company. These differences further underline that 'competition' does not signify the same activity in the different arrangements, but rather entails quite different actors, devices, metrics, procedures, and outcomes. This points to the importance in more carefully examining each particular configuration of interlinked valuation practices (e.g. Muniesa and Helgesson, 2013; Helgesson, 2016) and how these mediate between the science and market poles.

What valuations are involved in arrangements 1 and 2? Reading them from left to right we can deduce that these two arrangements involve valuations in the setting up of the development programs, the designing of the trials, the trials themselves, the valuation(s) involved when deciding to apply for market approval, and the valuations by the regulatory agencies assessing these applications. Then there are the valuations after market approval, where there is more than one drug approved. Here actors such as governmental agencies, insurance companies, physicians, and perhaps even patients may engage in valuations that assess and compare the drugs. The prices of the different drugs can figure in such valuations as well assessments of possible clinical differences. Such valuations can appear as highly formalized health technology assessments performed by governmental agencies or in less-formalized discussions between a patient and a physician. In conclusion then, the market competition alluded to in arrangements 1 and 2 involves a variety of valuation practices that can compare the competing drugs.

The configuration of valuations in arrangement 3 and 4 differ in many important respects from arrangements 1 and 2. This includes the differences in the valuations done when designing the trials, and how the trials themselves perform valuations to select a single compound. The many simulations used to specify the compound finder trial in arrangement 4 is a particularly pertinent example of such a difference as is the tournament-like competition performed by the compound finder qua 'valuation machine'. The major difference, however, lies in how arrangements 3 and 4 imply differently configured post-approval valuation practices. The valuations performed by governmental agencies, insurance companies, physicians, and so on become different since there are fewer treatments for price and/or performance comparisons. The valuation made to favor these arrangements over arrangement 1 and 2 rests precisely on the strategy of forwarding only one compound to the market, reconfiguring the valuations entailed in said markets.

The particular technique of valuation used to specify the compound finder trial in arrangement 4 is furthermore noteworthy. The tweaking of the compound finder parameters using simulations illustrates that there is a good probability it will perform this valuation at a lower cost and swifter than the sequence of RCTs relied upon in arrangement 3. Hence, the compound finder valuation machine is clearly configured in a context aimed to reduce trial costs, speed up the time to market, and to avoid market competition. The compound finder is part of a set of interlinked valuation practices that clearly link trial design to assumptions about what can provide the company with a favorable future market position. The valuations related to and performed by the compound finder mediate

between the science and market poles in particularly intense ways. The compound finder trial design is as made up of economic assumptions and considerations as it is made up of adaptive randomization algorithms and special techniques for statistical analysis.

Economic assumptions are always central in commercial drug development. One advantage of conceptualizing drug development as comprising interlinked valuations is that it can highlight how such matters can be entwined with the knowledge production (cf. Helgesson *et al*., 2016). The central point from this case is underscoring the variability with which interlinked valuations can have mediating roles between the science and market poles.

Reconfiguring What Knowledge Is Produced

We have already touched upon some epistemic aspects of the case, but we will now focus directly on how the arrangements differ in what knowledge they produce. A crucial implication of arrangements 1 and 2 is that they may produce sufficient knowledge about all compounds for them to be given market approval. This means that there will be a sufficient body of documented knowledge about each compound for assessment by regulatory agencies. This further implies the possibility of further accruing data regarding the clinical characteristics of each of the approved drugs as they are used in clinical practice. Activities around the market pole can contribute to knowledge production, more so than is possible in arrangements 3 and 4. In sum, arrangements 1 and 2 produce knowledge about more than one compound, and over time this can take place in several settings, including clinical practice.

In arrangements 3 and 4, far less knowledge is produced about the compounds not selected. This may be most extreme in arrangement 3 which involves a sequence of trials each testing a specific compound. As a consequence, this arrangement may be the epistemically most myopic, especially in the event it identifies a 'winner' in the first trial. Arrangement 4 is again different in the knowledge it will produce. As the compound finder trial progresses, more and more of the knowledge production will be focused on a single compound if any of them meet the criteria set in the trial algorithm. This means that less will be known regarding the compounds not selected. This feature is part of what makes the compound finder more efficient than a so-called conventional strategy using a sequence of RCTs.

The bottom line of this analysis is clear: arrangement 4 involving the compound finder is where the knowledge production is most clearly shaped by assumptions about what knowledge will have most value to the company. Knowledge about a single promising drug candidate, accrued at a lower cost, is considered more valuable than having knowledge about several potentially promising drug candidates. The trial algorithm is specified to focus on the epistemic attention in line with a valuation that stresses the value of knowledge in economic and market strategic terms. That is also why this arrangement is the most favored in the valuation performed in the case discussion we examined.

In sum, the different arrangements represent not only different configurations of interlinked valuations. They also have different properties regarding the knowledge they may produce. These are differences both in the wealth of knowledge produced and about what compounds/treatments knowledge is produced. The arrangements differ in how much becomes known about the compounds and where research attention is focused, and this all depends on how economic assumptions are incorporated into the valuation practices that guide the research endeavor.

Conclusion

The broad theme of this paper is how economic assumptions shape commercially driven drug development research. We have examined an industry-based bio-statistical discussion around a particular trial design, the compound finder, and looked at the valuations implied in this discussion. The examined discussion is focused on the properties of different trial designs in drug development programs. We identified four different arrangements, where each arrangement entails a particular configuration of interlinked assumptions and valuations (cf. Helgesson, 2016).

Our analysis showed several important differences in terms of possible epistemic outcomes of the drug development program. That is, which valuations determined what drugs would be available to consider for physicians and patients. This approach allowed us to examine the presence of economic assumptions in the valuations made for choosing and specifying trial design. We have to this effect particularly examined how these valuations can take into account assumptions about the future market and what provides the more favorable company position within the said market. In the form of such assumptions, the market can be made present inside drug trial designs. We have conceived this as the capacity of valuations to mediate between the science and market poles (cf. Callon, 1991; Miller and O'Leary, 2007). This adds to and extends on the previous research that has hinged on the importance of the regulatory assessments and the consequences these valuations have (e.g. Abraham and Davis, 2007; Eichler *et al*., 2008; Shea *et al*., 2013).

The point of this analysis is not simply to emphasize that economic considerations and assumptions are regularly present in the valuations that shape drug development, including the those that inform trial design (cf. Helgesson *et al*., 2016). Rather, the crucial point is that these mediations between the science and market poles can be differently configured and that this has important consequences for what knowledge is produced and what drugs are eventually introduced on the market and how they can be assessed.

This has been an exploration of how the economic is entwined with the scientific. We framed this in terms of how valuations are configured and interconnected within techno-economic networks. Such as, in this case, how an assessment of what is a good market position influences what counts as a good trial design. Seeing interconnected valuations as mediators between the science and market poles has been useful in illuminating how economic assumptions about the

'downstream market' can shape trial design, drug development, and ultimately decide drug availability (cf. Callon, 1991; Miller and O'Leary, 2007). Our introduction of a framework emphasizing the mediating role of valuations contributes to the collective arsenal of ways to examine how economic considerations and assumptions are shaping scientific endeavors.

There are many signs that different forms of ADTs will become more widely used in the years to come. The increased prominence of ADTs is in itself a sign of how desires to speed up drug development are imprinting themselves on trial design and the procedures for regulatory approval. The increased use of ADTs might not necessarily lead to a prominent use of the compound finder trial design. Yet, it will mean a larger dependence on trials where their properties can be tweaked using simulations and thus more aggressively shaped by, among other things, economic assumptions. The 'predictable uncertainty' provided by the simulations are, as Montgomery (2017) has argued, an important aspect of this emerging new mode of knowledge production. The use of simulations will likely mean that such trials actually can deliver on the promise of faster times to market that are cherished by proponents. As our analysis has indicated, it will probably in addition have other important consequences as regards allowing for a further influence of economic assumptions of where the epistemic attention is directed.

Acknowledgements

The overall project takes an interest in the experimental design of biomedical experiments as a site of valuations. The fieldwork for this sub-study was done by Helgesson. This version has benefited from comments by participants at a CSI seminar at Mines ParisTech, and in particular comments from Madeleine Akrich, Liliana Doganova, Alexandre Mallard, and Vololona Rabeharisoa. We would finally like to thank the editors Les Levidow and Kean Birch as well two anonymous reviewers for helpful comments on earlier versions.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This paper reports a sub-study within the 'Trials of Value: On the valuation practices in designing medical experiments' project funded by Riksbankens Jubileumsfond [grant number P11-0034:1].

Notes

[1]For a discussion on how the study valuations can be used to avoid separating the epistemic and economic as belonging to autonomous spheres, see Dussauge *et al.* (2015).

[2]21st Century Cures Act, H.R. 34, 114th Cong. (2015), section 3021. FDA published a draft guidance on ADTs already in 2010 (Food and Drug Administration, 2010).

[3]The approach used for statistical analysis is another area where there might be differences. Whereas traditional RCTs rely on so-called frequentist statistical analysis, ADTs might rely on so-called Bayesian inference. Yet, ADTs might also rely on traditional frequentist approaches (Chevret, 2012). An extensive discussion of such differences between RCTs and ADTs is beyond the scope of this paper.

[4]The specific details of the design actually involved two doses for each compound, which gave the trial a total of seven arms (two for each compound plus placebo). We have chosen to present the case in a simplified form as if it only had four arms, since the added complication of two doses per compound is unimportant for our overall analysis.

[5]One example: The rules for how different subjects are to be allocated to different treatments can have large consequences for how many patients end up with what might emerge to be considered a sub-par treatment.

Notes on contributors

Claes-Fredrik Helgesson is a professor in Technology and Social Change at Linkoping University, Sweden. His research interest concerns in broad terms the intertwining of economic organizing, science and technology. He works in the fields of economic sociology and science and technology studies (STS), currently often in the emerging field of valuation studies. Helgesson is co-founder and co-Editor-in-Chief of Valuation Studies, and is a co-editor with Isabelle Dussauge and Francis Lee of Value Practices in the Life Sciences and Medicine (Oxford University Press, 2015). His webpage is available at cfhelgesson.net.

Francis Lee is associate professor of Technology and social change at Uppsala University, Sweden. His research deals with valuations and politics of knowledge production. Of particular concern is how technological infrastructures—such as standards, algorithms, or big data—become part of knowledge production. He has published widely in science and technology studies (STS), and is a coeditor with Isabelle Dussauge and Claes-Fredrik Helgesson of Value Practices in the Life Sciences and Medicine (Oxford University Press, 2015). His webpage is available at francislee.org.

ORCID

Claes-Fredrik Helgesson http://orcid.org/0000-0002-6074-6088
Francis Lee http://orcid.org/0000-0002-7206-2046

References

Abraham, J. and Davis, C. (2007) Deficits, expectations and paradigms in British and American drug safety assessments: Prising open the black box of regulatory science, *Science, Technology, & Human Values*, 32(4), pp. 399–431.

Bijker, W. E. and Pinch, T. J. (1987) The social construction of facts and artifacts: Or how the sociology of science and the sociology of technology might benefit each other, in: W. E. Bijker, T. P. Hughes and T. J. Pinch (Eds) *The Social Construction of Technological Systems: New Directions in the Sociology and History of Technology*, pp. 17–50 (Cambridge: MIT Press).

Callon, M. (1986) Some elements of a sociology of translation: Domestication of the scallops and the fishermen of St-Brieuc Bay, in: J. Law (Ed.) *Power, Action and Belief: A New Sociology of Knowledge?*, pp. 196–233 (London: Routledge & Kegan Paul).

Callon, M. (1991) Techno-economic networks and irreversibility, in: J. Law (Ed.) *A Sociology of Monsters: Essays on Power, Technology and Domination*, pp. 132–164 (London: Routledge).

Callon, M. (1998a) Introduction: The embeddedness of economic markets in economics, in: M. Callon (Ed.) *The Laws of the Markets*, pp. 1–57 (Oxford: Blackwell).

Callon, M. (ed.) (1998b) *The Laws of the Markets* (Oxford: Blackwell).

Callon, M., Millo, Y., and Muniesa, F. (eds) (2007) *Market Devices* (Oxford: Blackwell).

Carpenter, D. (2010) *Reputation and Power: Organisational Image and Pharmaceutical Regulation at the FDA* (Princeton, NJ: Princeton University Press).

Chevret, S. (2012) Bayesian adaptive clinical trials: A dream for statisticians only?, *Statistics in Medicine*, 31(11–12), pp. 1002–1013.

Chuang-Stein, C. and Beltangady, M. (2010) FDA draft guidance on adaptive design clinical trials: Pfizer's perspective, *Journal of Biopharmaceutical Statistics*, 20(6), pp. 1143–1149.

Dussauge, I., Helgesson, C.-F., Lee, F., and Woolgar, S. (2015) On the omnipresence, diversity, and elusiveness of values in the life sciences and medicine, in: I. Dussauge, C.-F. Helgesson and F. Lee (Eds) *Value Practices in the Life Sciences and Medicine*, pp. 1–28 (Oxford: Oxford University Press).

Eichler, H.-G., Pignatti, F., Flamion, B., Leufkens, H., and Breckenridge, A. (2008) Balancing early market access to new drugs with the need for benefit/risk data: A mounting dilemma, *Nature Reviews Drug Discovery*, 7(10), pp. 818–826.

Elsäßer, A., Regnstrom, J., Vetter, T., Koenig, F., Hemmings, R. J., Greco, M., Papaluca-Amati, M., and Posch, M. (2014) Adaptive clinical trial designs for European marketing authorization: A survey of scientific advice letters from the European medicines agency, *Trials*, 15(1), pp. 383–392.

European Medicines Agency. (2007) *Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design* (London: EMEA).

European Medicines Agency and EFPIA. (2010) EMA/EFPIA 2nd workshop adaptive design in confirmatory trials. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2009/11/event_detail_000007.jsp&mid=WC0b01ac058004d5c3 (accessed 7 January 2015)

Fisher, L. D. (1999) Advances in clinical trials in the twentieth century, *Annual Review of Public Health*, 20, pp. 109–124.

Food and Drug Administration. (2006) *Critical Path Opportunities Report* (Washington, DC: FDA).

Food and Drug Administration. (2010) *Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics, Draft Feb 2010* (Washington, DC: FDA).

Fourcade, M. (2011) Cents and sensibility; economic valuation and the nature of 'nature', *American Journal of Sociology*, 116(6), pp. 1721–1777.

Godin, B. (2006) The linear model of innovation: The historical construction of an analytical framework, *Science, Technology & Human Values*, 31(6), pp. 639–667.

Helgesson, C.-F. (2016) Editorial note: Folded valuations?, *Valuation Studies*, 4(2), pp. 93–102.

Helgesson, C.-F. and Muniesa, F. (2013) For what it's worth: An introduction to valuation studies, *Valuation Studies*, 1(1), pp. 1–10.

Helgesson, C.-F., Lee, F., and Lindén, L. (2016) Valuations of experimental designs in proteomic biomarker experiments and traditional randomised controlled trials, *Journal of Cultural Economy*, 9(2), pp. 157–172.

Kjellberg, H. and Helgesson, C.-F. (2007) On the nature of markets and their practices, *Marketing Theory*, 7(2), pp. 137–162.

Krams, M. and Dragalin, V. (2014) Considerations and optimization of adaptive trial design in clinical development programs, in: W. He, J. Pinheiro and O. M. Kuznetsova (Eds) *Practical Considerations for Adaptive Trial Design and Implementation*, pp. 69–90 (New York: Springer).

Lamont, M. (2012) Toward a comparative sociology of valuation and evaluation, *Annual Review of Sociology*, 38(1), pp. 201–221.

Latour, B. (1987) *Science in Action: How to Follow Scientists and Engineers Through Society* (Cambridge: Harvard University Press).

Lee, F. (2015) Purity and interest: On interest work and epistemic value, in: I. Dussauge, C.-F. Helgesson and F. Lee (Eds) *Value Practices in the Life Sciences and Medicine*, pp. 207–223 (Oxford: Oxford University Press).

MacKenzie, D. (2006) *An Engine, Not a Camera: How Financial Models Shape Markets* (Cambridge: MIT Press).

MacKenzie, D. (2009) *Material Markets: How Economic Agents Are Constructed* (Oxford: Oxford University Press).

MacKenzie, D. and Millo, Y. (2003) Constructing a market, performing theory: The historical sociology of a financial derivatives exchange, *American Journal of Sociology*, 109(1), pp. 107–145.

MacKenzie, D., Muniesa, F., and Siu, L. (Eds). (2007) *Do Economists Make Markets? On the Performativity of Economics* (Princeton, NJ: Princeton University Press).

Marchenko, O., Fedorov, V., Lee, J. J., Nolan, C., and Pinheiro, J. (2014) Adaptive clinical trials: Overview of early-phase designs and challenges, *Therapeutic Innovation & Regulatory Science*, 48(1), pp. 20–30.

Marks, H. M. (1997) *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (Cambridge: Cambridge University Press).

Miller, P., and O'Leary, T. (2007) Mediating instruments and making markets: Capital budgeting, science and the economy, *Accounting, Organizations and Society*, 32(7–8), pp. 701–734.

Montgomery, C. M. (2017) From standardization to adaptation: Clinical trials and the moral economy of anticipation, *Science as Culture*, 26(2), pp. 232–254.

Moreira, T. (2012) *The Transformation of Contemporary Health Care: The Market, the Laboratory, and the Forum* (New York: Routledge).

Muniesa, F. (2012) A flank movement in the understanding of valuation, in: L. Adkins and C. Lury (Eds) *Measure and Value*, pp. 24–38 (Oxford: Wiley-Blackwell).

Pickering, A. (1995) *The Mangle of Practice: Time, Agency, and Science* (Chicago, IL: University of Chicago Press).

Rabeharisoa, V. and Doganova, L. (2016) Making rareness count: Testing and pricing orphan drugs. *i3 Working Paper Series*. Available at http://www.i-3.fr/en/workingpaper/making-rareness-count-testing-and-pricing-orphan-drugs/ (accessed 18 October 2016).

Roscoe, P. (2015) A moral economy of transplantation: Competing regimes of value in the allocation of transplant organs, in: I. Dussauge, C.-F. Helgesson and F. Lee (Eds) *Value Practices in the Life Sciences and Medicine*, pp. 99–118 (Oxford: Oxford University Press).

Shea, M. B., Roberts, S. A., Walrath, J. C., Allen, J. D., and Sigal, E. V. (2013) Use of multiple endpoints and approval paths depicts a decade of FDA oncology drug approvals, *Clinical Cancer Research*, 19(14), pp. 3722–3731.

Sjögren, E. (2006) Reasonable drugs: Making decisions with ambiguous knowledge, Published PhD diss, Stockholm School of Economics, 2006.

Sjögren, E., and Helgesson, C.-F. (2007) The Q(u)ALYfying hand: Health economics and medicine in the shaping of Swedish markets for subsidised pharmaceuticals, in: M. Callon, Y. Millo and F. Muniesa (Eds) *Market Devices*, pp. 215–240 (Oxford: Blackwell).

Tufts CSDD. (2013) R&D senior leadership brief: The adoption and impact of adaptive trial designs. *Tufts Center for the Study of Drug Development*. Available at http://csdd.tufts.edu/files/tuftscsdd_adaptive_trials.pdf (accessed 8 January 2015).

Will, C. and Moreira, T. (2010) Introduction: Medical proofs social experiments: Clinical trials in shifting contexts, in: C. Will and T. Moreira (Eds) *Medical Proofs, Social Experiments: Clinical Trials in Shifting Contexts*, pp. 1–13 (Aldershot: Ashgate).

Zuiderent-Jerak, T. and van Egmond, S. (2015) Ineffable cultures or material devices: What valuation studies can learn from the disappearance of ensured solidarity in a health care market, *Valuation Studies*, 3(1), pp. 45–73.