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Valuations of experimental designs in proteomic biomarker experiments and traditional randomised controlled trials

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ABSTRACT

This article examines the shifting conditions for biomedical knowledge production by studying trends in the design of biomedical experiments. The basic premise of the study is that the very act of establishing a research design entails a process involving a series of valuations where different values are evoked, ordered, and displaced. In focus is the articulation and ordering of what counts as central values in research design for two kinds of biomedical treatment trials, namely the traditional randomised controlled trial (RCT) and the emerging new form of biomarker trials used to assess biomarker/treatment combinations (BTTs). The empirical material consists of textbooks (RCTs) and journal articles (BTTs). We ask how these materials articulate the various scientific, medical, and economic values at play. Among the differences uncovered are a difference in relation to what counts as ethical in relation to prior knowledge, differences in the flexibility in design as well as the valuation of the risk for false positives and false negatives. More broadly, the study shows how textual accounts of *different ways of producing knowledge* are linked to partly *different valuations* of ethics, flexibility, and risk as part of establishing the research design of biomedical experiments.

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Introduction

The conditions for biomedical knowledge production are constantly being negotiated and renegotiated in contemporary society. Political, ethical, medical, scientific, and economic constraints and possibilities are constantly shifting. The questions 'What is worth knowing?' and 'What should we do to get there?' are continually handled using a variety of yardsticks for biomedical knowledge production. What is effective and efficient research? What are marketable research outcomes? What is ethically justifiable research? Viewed in this way, answers to the question 'What is valuable research?' become potentially multiple and divergent. Any answer to this question is contingent on a complex set of valuations. This article approaches the shifting conditions for biomedical knowledge by examining trends in the design of biomedical experiments and the intertwining, balancing, and hierarchisation of different values and measures of value for biomedical research. As such it attempts to shine light on shifting yardsticks, values, and pressures in the contemporary research landscape.

The premise of this study is that the very act of establishing a research design entails a process involving a series of valuations that are linked to the question posed above. We treat this process

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as an activity involving many different yardsticks of value. These can include such things as cost of materials, speed of discovery, scientific interest, clinical relevance, and market prospects. These yardsticks of value are intimately intertwined with ideas about research seen in terms of public goods, scientific goods, and/or commercial goods. Hence, we take an established design as the result of several valuations that deal with what is worth knowing, and what the appropriate means to generate this knowledge are. In short, we understand research design as a process that involves assessing different design parameters in light of, among other things, the expected knowledge outcomes.[1]

In this article we explore these issues by examining similarities and contrasts in design discourse between two different modes of experimentally assessing medical treatments: the traditional randomised controlled trial (RCT) and the emerging new form of biomarker trial used to assess biomarker/treatment combinations (BTT). We are interested in exploring how the design discourse related to these two different modes of knowledge production about medical treatments could shine light on some of the complex valuations that are part of biomedical knowledge production. The empirical material consists of textbooks on the design of traditional RCTs and journal articles on BTTs. In this investigation we ask how these materials articulate the various valuations and scientific, medical, and economic values that are at play in contemporary knowledge production.

This article centres on examining the articulation and ordering of what counts as central values in the process of research design for two kinds of biomedical treatment trials, namely the traditional RCT and the emerging BTT. Our focus on valuations in research design is a way to examine articulations about what knowledge is worth pursuing and what counts as the appropriate means for these endeavours. More broadly, our choice to focus on the design phase as well as on two different kinds of trials is done to facilitate an exploration of the various yardsticks mobilised in biomedical research. We thus see design as a site where we glimpse the making of different stakes in biomedical knowledge production.

The medical RCT has a history from at least the 1950s as the prime method for testing drugs (Marks 1997; Fisher 1999). The primary design feature of traditional RCTs is some form of randomisation where two or more treatments (or placebo) are distributed among a group of selected trial subjects. The randomised allocation of treatment to individual trial subjects is generally double blind. This means that neither the trial subjects (single blind) nor the staff seeing them (double blind) knows who gets what treatment when. Trial subjects are regularly patients, but they are selected with reference to criteria set in the trial protocol that, for instance, could exclude patients suffering from other complicating diseases. The randomisation in effect creates different subgroups, or trial arms to use the vernacular of trials, where each subgroup principally ought to be similar in all aspects but for the treatment they receive. On average, the populations of trial subjects in each arm would be similar due to the randomisation (one should expect same average age, same gender distribution, and so on).

Biomarker-based experiments on patients is part of what has been suggested as a trend towards '"biomarkerization" of health and disease' (Metzler 2010, p. 407), where biomarkers are seen as a route to provide better and more efficient diagnosis, prognosis, and treatment. At the most basic level a biomarker is something that points to a biological condition. A biomarker can be a bodily mark, such as the redness of eyelids to hint at anaemia (cf. Mol 1999). More commonly today biomarkers are seen as genetic or proteomic 'profiles' that can be used to classify patients and their disease using some sort of diagnostic or prognostic test. The iconic examples are the BRCA genes for predicting breast-cancer risk, and the screening for elevated levels of prostate-specific antigen for diagnosing prostate cancer. One often-expressed hope is that biomarkers can be used to stratify patients into subgroups where patients in each subgroup suffer from molecularly different types of cancer, or each subgroup has a different predicted response to a certain medication. In sum, the idea is that biomarkers can be used to identify therapeutically relevant differences among patients suffering from the same diseases such as, for instance, differences that express themselves in different responses to drugs. In keeping with these expectations of biomarker-based personalised medicine, a

primary idea of BTTs is that there is some sort of biomarker that can be used to stratify trial subjects into subgroups as part of the experimental arrangement.

Values and valuations as topics in the study of knowledge production

In science and technology studies (STS) there has been a long-standing interest in how social and cultural values are intertwined with research and development. Different studies have dealt with things such as racism (Winner 1980; Bowker & Star 1999; Fujimura 2013), accuracy and precision (Wise 1995; Mackenzie 1999), gender (Haraway 1988; Harding 1991), and calculation (Porter 1995), while other studies have focussed on the political economy of biomedical science through predefined notions such as capitalism and commodification (Shiva 1997; Waldby 2002; Sunder Rajan 2006; Rose 2007; Mitchell & Waldby 2010).

Our approach to examine research design as a process of valuation is inspired by the meeting of the fields of STS and studies of economic practice (Callon 1998; Callon et al. 2007). Here we are inspired by studies that have used concepts and sensibilities from STS for studying the intertwinement of technologies and economical practices such as in social studies of finance (MacKenzie & Millo 2003; MacKenzie 2009) as well as more broadly in research on calculative practices and performativity of economics, on how calculative devices and economic theories shape markets and agencies (Callon & Muniesa 2005; Callon et al. 2007; MacKenzie et al. 2007; Sjögren & Helgesson 2007; Cochoy 2008; Skærbæk & Tryggestad 2010).

In this article we build on the above research while simultaneously furthering a more inclusive approach to the study of values. We here take a pragmatic approach that sees all values, regardless if they are social, economic, or scientific, as *enacted* in the process of designing trials. One consequence of this approach is that it does not take values as static norms of various equally stable categories (economic, social, cultural, medical, scientific, and ethical) that influence action. This pragmatic approach to understanding values allow us to treat them as practical achievements where practices of valuation establish what values count and how various values are separated, ordered, or intertwined. We have elsewhere called this a valuographic approach (Dussauge et al. 2015). Such an approach works, for instance, well for the following scholars: Zelizer (1985, 2005), Appadurai (1986), and Stark (2000, 2009) who all have argued for analytically abandoning any sense of a priori and clear-cut distinction between (social and cultural) values and (economic) value. This is also similar to Bruno Latour's argument against social categories as points of analytical departure (Latour 2005).

One central advantage of this approach is that it takes seriously the complex and multifaceted practices that perform valuations. This opens up for understanding values as contingent as well as for examining how specific choices, devices, and orderings go into enacting certain values. The promise of this approach is to show how certain values (such as calculative or economic) become shaped and formatted through specific practices as part of the valuation. This enables us to study what values are articulated as desirable and what values are ignored or made absent. We understand this approach as a 'flank movement' to the study of values where they are seen as enacted and ordered in practices of valuation (Dewey 1939; Muniesa 2012).[2]

This study's focus on research design as a site where valuations are performed is thus closely tied to a pragmatic approach to values where values are seen as articulated, enacted ordered, and displaced in practices. In this, valuations are understood as enacting values rather than being determined by and therefore merely reflecting pre-stabilised values. This approach enables us to examine how different yardsticks are articulated, mobilised, and ordered in various aspects of research design. Moreover, it gives access to articulations as to what knowledge is seen valuable and on what grounds. Our choice to examine two different kinds of trials – traditional RCTs and emerging BTTs – further strengthens the valuographic approach in that it allows us to be sensitive to differences in the particular yardsticks articulated. In short, it allows us to examine differences in

what values counts, what knowledge is worth pursuing and what is seen as the appropriate means for these endeavours.

Examining textual accounts of valuation in design

We will in the following present an examination of design as it is expressed in textbooks (on traditional RCTs) and articles (on biomarker trials). Our focus has been to explore what they articulate in relation to trial design and the values and valuations at play in these articulations.

Regarding traditional RCTs, we have examined three textbooks. These were chosen on the basis of how well-used they seemed to be, something that was decided on the basis of how often they were borrowed at our local University library and how many University libraries in Sweden had used the books. Moreover, we did choose newer books in favour of older ones, as we wanted to know how design matters are articulated in a contemporary setting. All in all, this method gave us an indication concerning the books' relevance.

As BTTs are a less entrenched and emerging phenomenon in the biomedical research landscape, established textbooks in biomarker experiments were unavailable. Instead journal articles focussed on the design of biomarker experiments were used. To create a material on biomarker designs we searched for articles in the ISI web of science with 'biomarker* design' in the title that were published in the last five years (2008–2012). The focus was on biomarkers concerning humans. All articles that were published between 2011 and 2012 were included; articles published before 2011 that were cited more than once were included. From the remaining articles those concerning validation of BTTs were chosen in order to focus on experiments aimed to assess medical treatments, this as such focus is regularly the case in traditional RCTs.

The examination was conducted by thematically coding the relevant sections in three selected textbooks and a few articles were coded thematically using a software for coding, search, and retrieval. In a Fleckian (Fleck 1979) sense this means that we are investigating articulations of value in different parts of the knowledge collective concerning medical trials: sedimented textbook knowledge versus emerging scholarly discussions. As such this article does not deal in a proper comparison, but rather in exploring emerging articulations of value in biomedicine and contrasting those with more established ditto. Thus, our focus is on emerging trends in biomedical knowledge production.

Our examination of certain textual accounts provides one, albeit narrow, glimpse into the valuations that participate in shaping medical research. First, it should be readily acknowledged that the processes of trial design practice are far more convoluted and complex than any textual rendition of them. Second, the actual implementation and logistics of trials contain more contingencies than can be captured in a stabilised trial protocol (see, for instance, Jonvallen 2005; Helgesson 2010). Third, the trajectory of medical knowledge production is also contingent upon the practices of interpreting and (selective) publication of results, which may involve so-called publication bias (see, for instance, Dickersin et al. 1987). Yet, the narrow focus of the present study on textual accounts about trial design provides one step in the study of valuations in design practices. In this way, it turns attention to a part of medical experimentation that has been given little attention in social science research on clinical trials and the shaping of biomedical knowledge.

Valuations in design: from traditional RCTs to BTTs

Our investigation of the valuations in the design of medical experiments is done along four themes: (1) the broad-stroked characteristics of research design for RCTs and BTTs, respectively; (2) on the roles of uncertainty, ignorance, and absence of knowledge when designing trials; (3) design issues pertaining to scale, cost, and epistemic gain; and, finally (4) clinical relevance as a theme in trial design. For each of them we look both at how these valuations are discussed as regards design of traditional RCTs as well as for the emerging new form of BTTs.

The big picture

The pivotal design feature of an RCT is the randomisation of trial subjects to one out of two or more possible treatments (trial arms). The choice of treatments, influences – along with other design decisions – what kind of questions the trial can address. These questions could, for instance, be whether treatment A is superior to treatment B, or whether treatment A at least not is inferior to treatment B. Figure 1 is adapted from a textbook and shows three kinds of design for RCTs where the solid lines indicate the randomisation performed for allocating treatments to the trial subjects in a way that in effect creates two groups of patients.

On a highly general level a biomarker trial can test (1) the prognostic or diagnostic value of a biomarker or (2) a biomarker and treatment combination. In the following we focus on (2), the BTTs, as these have goals similar to traditional RCTs for testing treatments. In general, rather than asking, 'What treatment is best for these kinds of patients', which is a frequent question in RCTs, the question in a biomarker trial becomes 'What treatment and patient combination is best?' Thus, the biomarker trials we have chosen to discuss aim to test the efficacy of a BTT.

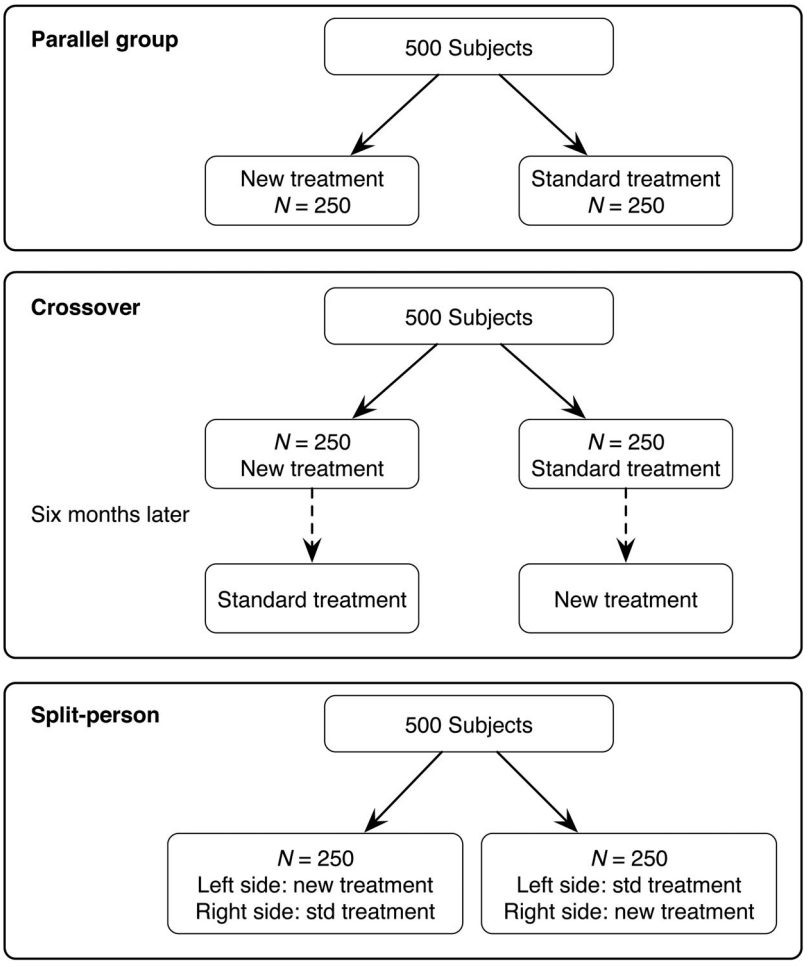

FIGURE 1. Three versions of trial design within the overall RCT design framework for testing different treatments. The split-person design could, for instance concern treatments distributed as an ointment where each trial subject gets two interventions one on different sides of their bodies (adapted from Hackshaw 2009, p. 59).

In a similar way to traditional RCTs, there is some sort of randomisation of the patient in BTTs. However, the random component of the trial is commonly performed *after* a patient stratification, and not, as in traditional RCTs, where it is often done at the very beginning of the trial. This later stratification is done in order to be able to test the efficacy of the BTT. The idea is that medical treatment could be tailored using patient classification on different genomic or protein expression profiles. Thus, a major difference in the design of traditional RCTs and the BTT is that the randomisation in the former aims to create similar groups in the different arms whereas stratifications in the latter are used to create subgroups of trial subjects that are dissimilar from one another. This means that in one case there is treatment stratification, while in the other there is patient as well as treatment stratification. As we will see, this difference has effects for what, and how, values are articulated in the design process. The pivotal design feature of biomarker trial is different from traditional RCTs, as the questions these trials ask are different than in regular trials.

Figure 2 shows a schematic image of the organisation of a biomarker-based trial designed to compare 'the MammaPrint 70-gene expression signature with a common clinical-pathological prognostic tool (Adjuvant! Online) in selecting patients with negative or 1–3 positive nodes for adjuvant chemotherapy in breast cancer'.[3] We can note that the randomisation occurs on the left-hand segment in the fourth row. It has been demoted from the start of the trial, where it would reside in a traditional RCT, and is now one step of many in clinical/medical knowledge production. Furthermore, it is only one out of the three initially identified patient strata that is made subject to randomisation, which randomises the trial subjects to one out of two decision rules for choosing the treatment.

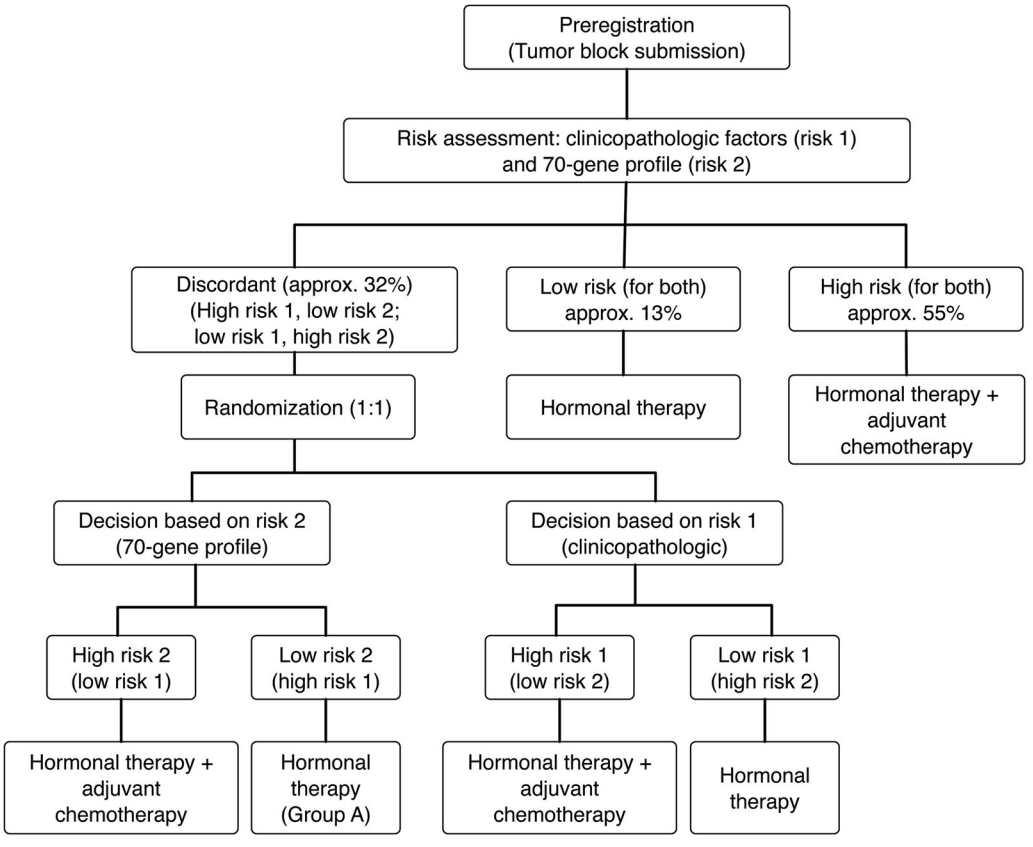

FIGURE 2. A schematic figure of the Microarray in Node-Negative Disease May Avoid Chemotherapy (MINDACT) trial design (adapted from Mandrekar & Sargent 2009, p. 4031).

The envisioned outcome of the design effort of a traditional RCTs is a protocol where the allocation of treatments to different subjects is to be done early in the trial using randomisation. In contrast, the BTT design depicted in Figure 2 works with stratifying trial subjects into more internally homogenous subgroups before a randomisation is performed as regards one such subgroup. As Mandrekar and Sargent (2009) argue in an article assessing multiple trial designs for biomarker validation:

> While there is no one-size-fits-all solution, it is clear that the choice of a clinical trial design is driven by a combination of scientific, clinical, statistical and ethical considerations. The current era of novel agents and targeted therapies such as small molecules, antibodies, and vaccines are mandating *intelligent clinical trial designs*. Well-designed retrospective analyses of RCTs, supplemented by prospective trials whenever possible, will hasten this important progress. (Our emphasis; Mandrekar & Sargent 2009, p. 4033)

In the case of biomarkers the design is envisioned to result in a protocol where the allocation of treatments to different subjects is to be informed by biomarkers during the trial. The advent of the discussions about biomarkers and personalised medicine ('targeted therapies') is thus argued to be 'mandating intelligent trial designs' that, as we show below, reshape knowledge-making practices in contemporary biomedicine. The articulations of principles for allocating treatments in the RCT textbooks are therefore different from those in the articles discussing the 'intelligent trial designs' in BTTs. This articulates a need to not only understand the drug in question but also a need to understand how it interacts with different kinds of bodies (as identified by biomarkers). One effect of the drive towards personalised medicine is, in this way, that the trial imagined in the regime of personalised medicine no longer solely tests the efficacy of a drug, but also attempts to test the interaction of the drug with specific bodily configurations. The resulting design, testing combinations of specified bodies and drugs, assumes a shape where different modes of stratification and sorting precede randomisation.

The differences in articulation of trial designs for RCT and BTT point to important tensions in the value practices of contemporary medicine. Below we examine further the articulation of values in relation to design discussions and these depict what could be recognised as specific versions of 'epistemic', 'ethical', and 'economic' values. The use of the single quotation marks further stand to remind us that what would count as say 'ethical' values indeed might differ between different trial design contexts.

On the roles of uncertainty, ignorance, and absence of knowledge when designing trials

> When an established treatment exists, it is unethical to give a placebo instead because this deprives some subjects of a known health benefit. (Hackshaw 2009, p. 12)

A central discussion in textbooks about RCT design concerns which treatments can be given to trial subjects in the two parts of the trial (the different arms). This relates to the objective of the trial. However, it is also, as illustrated in the quote above, intimately related to what can be considered to be known *prior* to the trial since this determines what can be considered an ethically viable trial. This, in turn, relates to the uncertainty as to what treatment is best for the patient that is considered to make it ethically possible to randomise different treatments among the trial subjects. In this way uncertainty is articulated as valuable to make a trial ethical. In these moments the epistemic values of uncertainty and ethical values are articulated in conjunction with one another:

> In addition there must be genuine uncertainty as to which of the options is best for the patient. It is this uncertainty which provides the *necessary equipoise* to justify random allocation to treatment after due consent is given. When a trial is planned, it is therefore clear that there must be considerable 'uncertainty' with respect to the relative efficacy of the 'therapeutic' options. Without this uncertainty, the trial should not commence. (Emphasis added; Machin & Campbell 2005, p. 149)

Trials are in this way understood as ethical if there is uncertainty about what treatment is best for patients. In the traditional RCT textbooks this is related to the notion of clinical equipoise. The

notion of clinical equipoise is articulated as a strong formulation of how prior knowledge affects what can be considered possible ethical options when selecting the treatments in the different arms.[4] Genuine uncertainty is expressed as a necessity for the trial to be considered ethical and is connected to the principle of clinical equipoise. Hence, an *absence* of knowledge about differences in treatment effects is articulated as vital for it being considered ethical to randomise between different treatments (or placebo).

Another epistemic valuation hinging on absences is the notion of bias. The *absence* of bias is considered highly valuable. Bias is understood as made possible by making sure that humans are not interfering in the conduct of the trial process: 'By removing all human influence from the random allocation process, possible biases are minimised' (Hackshaw 2009, p. 77). In RCT textbooks, the exclusion of human influence (and hence, what is understood as an ethical trial) is enabled through randomisation devices – in contrast with human interference. For instance, in one textbook it is said that:

> By the very term 'randomised', this design implies that the particular treatment given is chosen neither by the patient nor by the doctor, but by a randomisation device. (Machin & Campbell 2005, p. 149)

The use of a randomisation device is understood as making it possible to avoid biases related to undue human influence. Removing direct human involvement in treatment allocation makes the design more readily considered as able to produce unbiased results – and by extension outcomes that are objective and neutral. This focus on removing humans to enable objectivity can conceptually be understood as an expression of *mechanical objectivity* (Daston & Galison 1992). The concept mechanical objectivity expresses a non-intervening objectivity accomplished with the help of machines, technology, or other devices. The concept thus highlights the idea of machines as reliable in that they do not have any intentions nor do they intervene. Hence, they do not affect and disturb scientific practice. Mechanical objectivity stands in stark contrast to subjective judgements and decisions brought into scientific research by the researcher (Daston & Galison 1992).

In sum, the desirable epistemic starting point of RCTs hinge on uncertainty and ignorance among trial designers and clinical staff as tools for ethics and objectivity. Uncertainty about treatment effects is said to produce an ethical trial and ignorance about the allocation of treatments to trial subjects is argued to create unbiased objectivity. The ethical and epistemic cornerstones of biomedical knowledge production are therefore both related to absence of knowledge: absence of knowledge about differences in treatment effects, and absence of knowledge about which treatment patients receive.

The epistemic starting point and what counts as ethical is different in the case of BTTs. Prior knowledge about the biomarker and its possible relation to treatment effects is utilised in trials testing BTTs to stratify patients into different treatments (arms). The use of biomarkers for patient stratification thus shakes the above-delineated cornerstones of RCTs to their core. In a trial where a BTT is tested, there has already accumulated a large amount of biological knowledge about the predictive abilities of biomarkers prior to the trial, which makes the 'genuine uncertainty' of the RCT less strong. Thus, both the uncertainty about treatment effects and the ignorance of patient distribution are jettisoned in BTTs. In this vein, biomarker trials muddle the ethics anchored to the notion of equipoise and mechanical objectivity of RCTs.

In both traditional RCT design and BTT design, previous knowledge is viewed as raising ethical concerns. One discussion of the ethics of biomarker-based trial designs is how to handle the treatment of the patients about whom there is prior knowledge. Here the purported knowledge of the effectiveness of different treatments is seen as leading to two 'clinical dilemmas'. First, the notion of not knowing, of genuine uncertainty are in these discussions shifted to statistical and organisational handling of patients that are 'pan resistant' to the trial drugs. Second, the notion of knowledge informing the trials, rather than uncertainty and absence of knowledge, is articulated as being a problem in that biomarker-based knowledge about the patients is seen as rapidly changing, making both knowledge and uncertainty moving targets that need to be handled by 'novel statistical methods'. In biomarker-based trials there are, thus, new ethical dilemmas that need to be handled:

> One of the clinical dilemmas that arises in studies of therapeutic biomarkers is the problem of what to do for patients in whom the biomarkers predict resistance to all of the drugs tested. We suppose that in preparation for a prospective randomized trial, such as we propose, investigators have some confidence in the stratification, based on a mix of biological knowledge and some data indicating the way the biomarkers predict response in observational studies of the outcomes of treatment given by physician's choice. The question of whether to include the 'pan-resistant' patients in the main trial, contributing to the hypothesis testing, depends on the trade-off of increased degrees of freedom for the tests versus capitalizing on an unexpected result (e.g., via a contribution to rejecting the intersection null). When theory and prior data suggest that there are no differences in treatment outcomes in a sub-group, there is little justification in spending degrees of freedom on the small chance of a surprise. So we would exclude them from the main trial. Since their biomarker measurements are already taken, they can be enrolled in an auxiliary trial in which we randomize them among the *K* treatments. (Lai et al. 2012, p. 153)

Thus, in biomarker-based trials the notions of equipoise and genuine uncertainty become replaced by different ethical framings that are tied to the biomarker-based prior knowledge. Rather than focussing on the importance of genuine uncertainty and absence of knowledge as the ethical bases of a trial, the discussion of the ethics of biomarker trial designs emphasises how prior knowledge based on biomarkers needs to be actively brought in as a ground for action. In this way, previous knowledge, as in traditional RCTs, is articulated as a problem. In the case of BTTs it is not absence of knowledge that is the cornerstone of ethics, but a knowledge-based and ethical patient sorting. Thus, there is a shift from randomisation as tied to the ethics of equipoise to an ethical framing that encourage knowledge-based sorting. Going from an ethics of uncertainty to an ethics of knowing shifts the registers of vigilance needed: vigilance of the purported uncertainty versus vigilance of the state of knowledge. A negative epistemics of ignorance is replaced by a positive epistemics of knowing.

Let us now take stock of what emerges when setting the textual accounts regarding the design of RCTs and BTTs side by side. There is a clear difference in the articulation of what counts as ethical. Our textbook sources on RCTs emphasise how the design must be such that there is a genuine uncertainty about the relative efficacy of the alternative treatments. The notion of clinical equipoise is to this effect put forward to specify what should characterise the design of the trial so as to make it ethical on behalf of the trial subjects. In the articles about BTTs we can discern a shift where prior knowledge reframes what is seen as ethically salient. Here genuine uncertainty is replaced by biomarker-based knowledge that should lead to a choice between different treatments, and what to do for patients for whom no treatment works. Another striking aspect of the difference discerned relates to mechanical objectivity and randomisation. Whereas randomisation is an espoused aspect for producing ignorance in the textbooks on RCTs, the texts on BTTs instead highlights biologically and statistically informed choices and stratifications as part of the design of an experiment.

Design issues pertaining to scale, cost, and epistemic gain

Deciding on the number of trial subjects involved, i.e. the sample size, is a crucial trade-off in trial design that interweaves several different registers of value. Three different reasons for why the size of the trial is an important concern are invoked: the possible research results, economic resources spent, and fairness. In other words, in articulations about sample size the epistemic, ethical, and financial sides of a trial appear as closely connected.

One trade-off central in our material is the one between research results and the use of time, as well as economic and human resources. This trade-off, then, brings forward one way in which scientific and economic registers of value are intertwined:

> A common situation is one where the number of subjects (often patients) that can be included in a trial is governed by non-scientific forces such as time, money or human resources. With a predetermined (maximal) sample size, the researcher may then wish to know what probability he or she has of detecting a certain effect size with a trial confined to the size. (Machin & Fayers 2010, p. 193)

Another facet of the scale trade-off is how clinically important differences might be missed with a too small trial, and that an unnecessary large trial might delay the market introduction of a superior treatment:

> If there are too few subjects, a clinically important difference may be missed. If there are too many subjects, resources could be wasted and a delay may occur in offering a superior treatment to future patients. (Hackshaw 2009, pp. 65–66)

As indicated in the quote above, a central reoccurring trade-off in the textbooks on traditional RCTs is the one related to sample size: having too few subjects might mean that the trial produces no results whereas having too many subjects implies unnecessarily high expenses. Research results are hence repeatedly articulated as being balanced against resources. These quotes illustrate how many different considerations are made part of determining a trial size. Too many subjects would mean that recourses are wasted unnecessarily, but having too few subjects is articulated as not spending enough resources to generate statistically significant (and conclusive) research results.

Another scale trade-off intertwines financial aspects with what is considered to be fair for patients and participants. Here, not only research results (a clinically meaningful difference) are staged as important, but also the ethical treatment of the patients. Fairness is articulated as being related to both the possible discomfort of those participating in the clinical trial and to the number of patients getting a more effective treatment. This can be illustrated with the following quote:

> A small trial with no chance of detecting a clinically meaningful difference between treatments *is unfair* to all the trial participants who are subjected to the risk and discomfort of the clinical trial. On the other hand, recruiting too many participants is a waste of resources and *may be unfair* if, for example, a larger than necessary number of patients receive the inferior treatment when one treatment could have been shown to be more effective with fewer patients. (Emphases added; Machin & Campbell 2005, p. 179)

In this context, what is ethical is not linked to the notion of equipoise discussed above, but to the knowledge about differences in treatment effects that the trial might or might not uncover. If the trial is too small, it will not be fair for trial subjects as they are exposed to unnecessary risks and discomforts during the trial without it producing any subsequent epistemic gain. In this way unnecessary denotes that the trial should be of value for the trial patients – and in extension for patients 'out there'. A too big trial might be unfair, on the other hand, since more than the necessary number of trial subjects might receive a treatment that we subsequently would identify as the inferior treatment. Deciding on scale (sample size) is hence an instance where the issue of the possibility to get unequivocal results is not only linked to the resources spent. It is also articulating a link between the welfare of the trial subjects and the possible epistemic gains of the trial. It is further here the notion of (statistical) power is central in RCT design since it denotes the probability that an effect is detected, provided that this effect truly exist: (We could think of power as the probability of an epistemic gain under the assumption about reality to the effect that such an epistemic gain is there to be made.)

> This is why it is important to try to detect the smallest clinically worthwhile effect, with 80 or 90% power, in order to have an appropriately sized study. (Hackshaw 2009, p. 74)

BTTs and scale, on the other hand, implicates both the idea of personalised medicine, but also the idea about so-called flexible trial designs. One of the promises of biomarker-based trials is to combat the high failure rate of trials, by targeting subsets of the population identified by biomarkers. The quotes below illustrate how innovation in biomarker-based trials are articulated as a panacea for the high failure rates of trials, but that the large sample sizes needed for trials of personalised therapies also need adaptive designs to shave off costs and adapt to evolving biomarker knowledge. In our material, innovation in trial design is articulated as a trade-off between process-efficiency/economic costs and the epistemic risk of false positives:

> Traditional clinical trial designs for development and validation of biomarker-guided therapies, as described for example in [2], often require large sample sizes; moreover, they cannot adapt to evolving knowledge about biomarkers. AR [a type of adaptive design] designs … 'which allows researchers to avoid being locked into a single,

> static protocol of the trial', can 'yield breakthroughs, but must be handled with care' to ensure that they do not 'inflate the risk of reaching a false positive conclusion', … 'The [adaptive] approach has been controversial, but is catching on with both researchers and regulators as companies struggle to combat the nearly 50% failure rate of (cancer) drugs in large, late-stage trials'. It is hoped that innovative designs can 'drive down the cost of clinical trials 50-fold' in comparison with traditional designs for the development of personalized medicine, otherwise 'drug companies (won't) be interested in taking the risk of developing a drug for these small number of patients' [34]. (Lai et al. 2012, p. 149)

Here biomarker-based adaptive designs are described as yielding epistemic breakthroughs and cost savings. An interesting register of value in the material on biomarker trials focusses on the flexibility and rigidity of trial designs. Where the biomarker-based designs are heralded as a more modern and flexible way to organise trials, the traditional RCTs are described as fixed and rigid (Lai et al. 2012, p. 149).

This links epistemic and organisational registers of value. Where organisational flexibility of the trial is made possible by an epistemic change, where questions, randomisations, and trial designs can shift. However, there is also an epistemic anxiety linked to the aforementioned jettisoning of the rigid RCT protocols, that are still described as the gold standard: 'the gold standard … continues (appropriately) to be a prospective RCT … ' (Mandrekar & Sargent 2009, p. 4028). BTTs is tied to a similar trade-offs as regular RCTs, i.e. attempting to minimise the sample size and number of events with the risk of increasing false certainty:

> Preliminary work suggested that the [x] design may be superior to [y] design in terms of the number of events (and hence the total sample size) required (while keeping all the parameters the same for both designs) … (Mandrekar & Sargent 2009, p. 4032)

Thus, the major trade-off between biomarker-based designs – i.e. 'targeted/enriched', 'unselected/all-comers design', and 'hybrid designs' (Mandrekar & Sargent 2009, p. 4028) is articulated as being one of costs versus epistemic risk. However, the trade-off is not solely tied to the scale of the trial, but also introduces innovation in trial design as a possible route to cost savings.

Summing up, there are major differences in how issues pertaining to scale, cost, and epistemic gains are articulated in the design of RCTs and BTTs, respectively. Cost is a highly present register of value in both cases, but it is differently linked to other facets. The possibility of a true epistemic gain, to take one example, is in RCT design strongly linked to trial size and the notion of power to safeguard against the risk of false negatives (i.e. the risk of not finding a treatment difference whereas there is one to be found). In BTTs, on the other hand the possibility of an epistemic gain is linked to flexible designs while safeguarding against the higher risk of false positives (i.e. the risk of falsely identifying a treatment difference whereas there in fact is none). Furthermore, issues of scale are further linked to ethical registers of value in expressions of the desirability to not involve an unnecessary large number of patients trial subjects in light of the possible epistemic gain (see also previous section).

Clinical relevance as a theme in trial design

The notion of clinical relevance is recurrently evoked as an important value in the traditional RCT textbooks. This notion denotes how the trial might produce knowledge of importance to the everyday practice of medicine. It is brought to the fore in discussions on what to measure as treatment outcomes as well as when the epistemic quality of the trial results is brought up:

> For many trials, the choice of endpoint will be easy, for example death, the occurrence or recurrence of a specific disease, or a change in habits. The main endpoint should be *clinically relevant* to both the trial subject and the researcher. (Hackshaw 2009, p. 61)

> There are circumstances where small *therapeutic advantages* may be worthwhile demonstrating, particularly in the fields of cardiovascular disease and cancer. In terms of trial size, the smaller the potential benefit, essentially

> the effect size, then the larger the trial must be in order to be reasonably confident that the small benefit envisaged really exists at all. (Machin & Campbell 2005, p. 150)

Financial or commercial aspects of the trial results are not part of the textbook discussions related to clinical relevance. Instead epistemic gains from a trial are articulated as if it was a public good: the outcome of the research is measured against its relevance for practitioners and patients (and not say, a pharmaceutical company). In this sense, it is not merely a research design that should be of value for the research community that is desired, but research that is of relevance, too, for society. Hence, clinical relevance is articulated as a public good. The question(s) posed must have important consequences in that the answer should inform research and/or *influence clinical practice in a meaningful way* (Machin & Fayers 2010, p. 25). However, in discussing clinical relevance, the financial aspect of trial cost do implicitly appear since clinical relevance is related to trial size (see the latter of the two quotes above and the previous discussion on power). In this way, financial aspects are not explicitly discussed but are still brought to bear on the register of value pertaining to clinical relevance.

The notion of clinical relevance is somewhat differently configured in the realm of BTTs. The core idea of BTTs is that it is worthwhile to assess the efficacy of BTTs. The premise for this is that the efficacy of treatments may vary for different patients and that patients can be identified through the use of biomarkers. Hence, BTTs are aimed to produce knowledge about the efficacy of treatments in relation to patient stratifications that possibly could be replicated in clinical practice:

> Advancing new discoveries from the bench to the bedside is the ultimate goal of clinical and translational research. The concept of predictive biomarkers moves the field a step closer toward individualized medicine, whereby individuals who are likely to have a favorable clinical outcome such as improved survival and/or decreased toxicity from a treatment can be prospectively identified. (Mandrekar & Sargent 2009, p. 4033)

BTTs thus not only reconfigure how clinical relevance is understood in the realm of trials, but ties this to a reconfiguration of how clinics are to make use of the knowledge thus produced. In short, clinics are to use biomarkers to match patients to treatments on the basis of knowledge produced in BTTs.

The clinic can hence both appear as a stand-in for the epistemic gain that the trial is designed to produce, as in the articulations about favouring clinically relevant endpoints. Yet, it can also become a matter of ethics in trial design where the treatment of patients in the trial becomes the focus. By evoking yardsticks relating trials to the clinic, certain valuations and certain epistemic interests are presupposed and favoured in the trial design.

In traditional RCTs, then, clinical relevance is evoked as a way to discuss the epistemic gain from a trial as a public good. This is not that different from one of the ways the clinic is made relevant in BTTs. Yet, in the latter case it appears also in other guises.

Concluding discussion

We have examined articulations about valuations entailed in the design of two kinds of biomedical experiments for testing treatments, namely the traditional RCT and the emerging kind of trials that assess BTT. Examining textbooks on the design of traditional RCTs and journal articles on BTTs, we have asked how these articulate various valuations and scientific, medical and economic values in contemporary knowledge production. Three different themes have been discussed: first, we discussed the roles of uncertainty, ignorance, and absence of knowledge when designing trials. Here, we discussed what is articulated as an ethical basis for the different trial design. We also noted how the newer BTTs appear to represent a shift from emphasising a stable protocol and something akin to mechanical objectivity to flexibility and adaptability. Second, we discussed trial design issues pertaining to scale, cost, and epistemic gain. In this section we considered how trial cost, epistemic gain, and trial subject ethics appear as different yet linked registers of value that are to be balanced when deciding the scale of the trial. We further noted that there is a different emphasis between traditional RCTs and new BTTs as regards the risks of false negatives and false positives. Third, we examined to

the notion of clinical relevance and the desired epistemic output of the different trials. In this discussion, we discussed how valuations of clinical relevance are articulated as having to do with the epistemic gain as a public good (rather than, say, a commercial value).

The basic premise of the study was that the very act of establishing a research design entails a process involving a series of valuations where different values are evoked, ordered, and displaced. The values related to research design has been examined with a valuographic approach; by seeing values as ongoing achievements established through articulations, negotiations, and orderings. In doing so, we have discussed what knowledge is articulated as worth pursuing as well as what means are deemed appropriate. Moreover, we have been able to see what registers of value are central in such valuations. Our reading of textbook accounts about the design of RCTs and articles about the design of BTTs indicate consequential differences as to how certain valuations are made in the design work – something that has consequences for what knowledge is seen as valuable.

The valuations described in our textual sources have, as depicted above, been related to assessing the possibility to produce results with some certainty and clinical relevance, and to relate the results to the costs of producing them. We have, moreover, discussed how the trend of personalised medicine includes a significant shift. In the design of the traditional RCT a stable protocol and genuine uncertainty are measures related to the value of something akin to a mechanical objectivity and a trial subject ethics of not knowing. In the design of the new emerging BTT, the adaptable protocol evokes values of flexibility and where the changing knowledge about trial patients is seen as an ethical dilemma vis-à-vis the trial subjects. In short, the valuations that are part of trial design differ in non-trivial ways between the two kinds of ways to perform biomedical experiments examined.

Our results suggest that the valuations in design entail important links between different versions of certain values. Several differences in what counts in the design of the traditional RCTs and emerging BTTs indicate that the valuations in design are interlinked in intricate ways. Consider, for instance, the specific and more complex allocation of trial subjects to treatments in the BTT trial involving booth stratifications and randomisation discussed previously (see Figure 2). The discussion of such a design tied both to a new assessment of what counts as clinically relevant results and a new understanding of the ethics related to trial subject enrolment. In short, the valuations in such a design interlink specific versions of 'epistemic' and 'ethical' values. Similarly, the discussions of the cost of an experiment often hinges on trial size and is entangled with both issues of trial subject ethics as well as with the quality of the knowledge thus produced. Hence, specific versions of 'economic', 'ethical', and 'epistemic' values are interlinked in such valuations. Different kinds of experiment designs not only entail a certain configuration of *how the experiment* is going to be performed, they also entail certain configurations of the valuations. As a consequence, different kinds of trial designs appear to enact a different composite of what counts as 'ethical', 'economic', 'epistemic', 'clinically relevant', and so on.

This study has entirely relied upon textual sources regarding research design. This limited focus has nevertheless allowed us to depict the above summarised pertinent differences between traditional RCTs and BTTs in how different registers of values are evoked. It is certainly reasonable to deduce that the practices of research design are more convoluted and furthermore involve commercial assessments not so readily discussed in the textual accounts we have examined. It is further true that medical research is shaped by practices, including valuation practices, in other sites of biomedical experimentation, such as when deciding if the results of a completed study should be published or not. Thus, we have in this study been able to map a few of the valuations that participate in shaping the biomedical knowledge production. Yet, the focussed study of textual accounts has nevertheless clearly exposed how certain valuations related to the design of biomedical experiments differ somewhat between different kinds of design.

Different ways for conducting research involve not only differences in how things are done, but also differences in the valuations that are part of shaping this research. This is an important general lesson that goes far beyond the specific valuations of research design examined here. To us, this opens up for empirically examining a number of research fields. What valuations are part of

determining what knowledge is worth pursuing? Given the power of knowledge, this is indeed a line of inquiry worth pursuing.

Notes

1. Within STS there is a long-standing tradition of doing empirical studies on the practices of medical research (Fujimura 1987; Epstein 1996; Löwy 1996; Keating & Cambrosio 2006). However, the practices of experimental research design has not been the object of extensive empirical study, which also holds for the recent and growing social sciences studies about RCTs in medicine (Fisher 2009; Petryna 2009; Sismondo 2009; Helgesson 2010; Will & Moreira 2010).
2. The growing interest in valuation can be seen in different topics, from markets, to tomato tasting (Helgesson & Kjellberg 2013; Helgesson & Muniesa 2013; Heuts & Mol 2013; Kjellberg et al. 2013).
3. http://www.agendia.com/clinical-trials-mindact/
4. The notion of clinical equipoise was introduced in the 1980s and has also been subject to some criticism in that it puts too strict restrictions on what should be considered ethically viable options.

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No potential conflict of interest was reported by the authors.

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