European Journal of Analytic Philosophy EuJAP | Vol. 17 | No. 2 | 2021
https://doi.org/10.31820/ejap.17.3.2

ADAPT TO TRANSLATE – ADAPTIVE CLINICAL TRIALS AND BIOMEDICAL INNOVATION

Daria Jadreškić[1]

[1] University of Klagenfurt

Original scientific article – Received: 16/05/2021 Accepted: 26/09/2021

ABSTRACT

The article presents the advantages and limitations of adaptive clinical trials for assessing the effectiveness of medical interventions and specifies the conditions that contributed to their development and implementation in clinical practice. I advance two arguments by discussing different cases of adaptive trials. The normative argument is that responsible adaptation should be taken seriously as a new way of doing clinical research insofar as a valid justification, sufficient understanding, and adequate operational conditions are provided. The second argument is historical. The development of adaptive trials can be related to lessons learned from research in cases of urgency and to the decades-long efforts to end the productivity crisis of pharmaceutical research, which led to the emergence of translational, personalized, and, recently, precision medicine movements.

Keywords: *adaptive clinical trials; randomized controlled trials; reliability; urgency; precision medicine; translational medicine; the productivity crisis*

Correspondence: daria.jadreskic@aau.at

1. Introduction

Adaptive clinical trials have been at the forefront of the efforts to mitigate the ongoing coronavirus pandemic due to their shorter duration and flexible design, which allows for accelerated assessment and the timely implementation of new vaccines and therapies (WHO 2020; Stallard et al. 2020; Branch-Elliman, Elwy, and Monach 2020; London and Kimmelman 2020). Adaptive trials are a subset of randomized controlled trials (RCTs), in which one or more features of the design can be changed during the trial's course based on interim results from the data accumulated early on.[1] Although they use control groups and randomization of patients to either the experimental or the control treatment, they differ from the standard RCTs by the absence of a fixed design. A fixed trial is first designed, conducted, and then analyzed upon completion, with no intermediate steps. In cases in which quick action is needed and standard RCT evidence is not available and takes too long to acquire, observational and other types of evidence need to provide temporary guidance. Adaptive design trials enable this by generating results based on observing patient responses and conducting interim analyses, in this way integrating evidence from experimentation with observational evidence and preclinical data.

Recently, London and Kimmelman have argued for the usage of multi-arm and seamless adaptive design trials, stating that "one lesson of the current outbreak is that expeditious research in a crisis situation is feasible" (2020, 477). If responsible expeditious research via adaptive design is feasible, should its methodology be used more widely, also in non-crisis contexts? To what extent are adaptive trials a valid, or even superior alternative to fixed RCTs in clinical research? If yes, on which grounds and under what circumstances? A conjoined ethical and epistemological discussion is in place. The aim of this paper is twofold: to outline some of the advantages and limitations of adaptive trials, and to specify the conditions that contributed to their development and implementation in clinical practice. This will make a case for their usage, but not in all contexts.

The first argument advanced in this paper is normative: responsible adaptation should be taken seriously as a new way of doing clinical research, but only insofar as a valid justification, sufficient understanding, and adequate operational conditions for the introduction of adaptive measures are provided. The most common obstacles to their implementation are local and practical, rather than general and principled. The greatest danger to the integrity of clinical research is shared across

[1] There can be non-randomized and uncontrolled trials, including adaptive trials, but they do not satisfy regulatory standards and their limitations are well documented.

different designs: it is, on the one hand, the ineliminable uncertainty of experimenting, and on the other, it is the intrusion of unwanted bias, such as sponsorship bias, or more broadly, preference bias (Wilholt 2009). However, both dangers hold for fixed and adaptive trials alike, and should not downplay positive aspects of adaptation.

The second argument is historical: the presence of adaptive trials as one of the potential drivers of biomedical innovation can be related not only to lessons learned from research in cases of urgency, but also to the decades-long efforts to end the productivity crisis of pharmaceutical research, which led to the emergence of translational, personalized, and more recently, precision medicine movements. These efforts have motivated new methods, organization, and relations between research stakeholders. Biomedical innovation has been spurred by investments in education and training in translational research, promotion of interdisciplinarity, collection of a variety of data- and bio-banks, developments in bioinformatics, calls for inclusion of patients in healthcare decision-making, and a general focus on the (re)organization of basic-clinical research interface via private-public partnerships. This has contributed to a broadening of clinical research teams to include experts in bioinformatics, statistics, and other big data skills which have enabled, among else, innovations in clinical trial design.

The ratio of randomization to different treatment arms in adaptive trials may not be equal or consistent throughout the trial's course, so the term 'adaptive' sometimes primarily characterizes randomization, such as in "outcome-adaptive randomization" (Berry 2011). Other adaptations include changes in sample size, treatment dose, or patient allocation ratio (Pallmann et al. 2018, 2). Adaptation can also mean abandoning treatment arms, stopping the trial early because of evident success or a lack of efficacy, or identifying and recruiting patients who are most likely to benefit from the treatment. Adaptive trials can assess several treatments in a single trial, or seamlessly merge different trial phases into only one trial. Adaptations need to be preplanned and modeled before the onset of the trial to preserve its integrity and generate valid results (Pallmann et al. 2018, 10-11). Without planning, rigorous execution and analysis, there is an increased risk of introducing bias into the trial. Results can be difficult to interpret due to a higher tolerance for false positives, in other words, for cases of observed beneficial effects whose cause is wrongly attributed to the experimental treatment.

A departure from the fixed RCT standard predates the coronavirus pandemic. Adaptive trials have been used both in urgent circumstances such as the 2013-2016 Ebola virus (Henao-Restrepo et al. 2017; Calain

2018) and earlier the AIDS epidemic (Epstein 1996), but also for evaluating therapies in the domain of precision medicine. If the mechanism of the experimental intervention is well understood, for example, because of the possibility to match therapies with subgroups of patients based on genomic data, the trial can be designed to recruit only patients who will benefit from the treatment. Adaptive trials are thus being increasingly used for evaluating the efficacy of cancer therapies and other targeted interventions (Riley 2016; Garralda et al. 2019), and both EMA and FDA have included them in their regulatory schemes (EMA 2017; FDA 2019).

I section 2, I discuss two cases of adaptive trials: the azidothymidine (AZT) trial in the 1980s and Ebola ca Suffit! trial in 2015. These two trials present milestones for the usage of adaptation in the context of crisis. Motivations for conducting adaptive trials are identified, as well as the trade-offs permeating the decision to rely on them. Section 3 puts forward the bulk of the normative argument. I draw on London and Kimmelmann's (2020) lessons from the ongoing coronavirus pandemic to show that reliable adaptation is alive and well and that the tension between reliability and speed in clinical research can be dissolved, but only under adequate operational conditions for running large-scale, multi-arm adaptive trials. I use the notion of operational exceptionalism to depict the current situation in which adaptive trials can be successfully implemented only via "carefully orchestrated protocols" (London and Kimmelmann 2020, 477) in big research centers with close ties to industry and policy makers. In section 4, I present a cluster of adaptive measures developed as part of clinical research in precision medicine. New conditions under which adaptations can be preferred to fixed RCTs are identified. In section 5, the historical path to precision medicine is outlined. The focus is on the emergence of different biomedical initiatives in the big data era that have brought new ways of generating and assessing evidence, together with innovations in clinical research which are following up on the advances.

The concluding section sums up the two arguments. Since the material, infrastructural, computational, and organizational conditions for conducting adaptive trials are at hand more than ever before, the case for their wider usage is made stronger. Still, there are practical and logistical drawbacks to the possibility of successfully implementing complex interventions such as adaptive trials across the board. Their recent successful uptake in assessing Covid-19 vaccines and treatments gives us much reason for optimism, but almost as much for caution. Adaptation should not mean that anything goes, but rather that everything is in place to make a balanced judgment based on available evidence and cooperative engagement of various interested parties. Inevitably, these hard choices are made in face of great uncertainty and nested interests.

2. Adaptive Trials in Epidemics

In this section, I present two cases of adaptive trials conducted in the urgent context of an ongoing epidemic. In these cases adaptation was chosen as a consequence of exceptional circumstances, prompted by ethical reasons to balance potential harms in a particular way.

The first case is the controversial AZT trial during the AIDS epidemic in the late 1980s, known for the groundbreaking role played by patient advocacy and citizen science (Epstein 1996). The first drug for AIDS, azidothymidine (AZT), was approved more quickly than subsequent therapies, in part because of the pressure for quick approvals coming from patients' advocacy groups and the fact that there was no efficient therapy available. Although planned as a fixed, double-blinded, randomized, placebo-controlled trial, control groups were eventually excised from the trial so that more patients could get the medication immediately. This practice is considered adaptive by clinical research standards, as volunteers would normally be randomly assigned to either the treatment or the control arm equally, and the randomization ratio would be fixed until the end of the trial. Because there was no therapy for AIDS and the patients' prospects were poor, many of them felt that they had nothing to lose. Potential harms associated with accelerated access to the experimental therapy were considered acceptable for many patients seeking help. In a record time, AZT was approved in 1987 after it had shown beneficial effects. However, the drug was not as successful as it was first thought. A three year follow up study of its effectiveness conducted on two thousand patients showed that patients in the placebo group were more likely to survive the three years of study than patients on AZT and that the drug had serious side effects and almost no benefits after a certain period of usage (Crewe 2018). It was later shown that AZT has beneficial effects, but only in combination with other medications, which is how it is still being prescribed and used.

The AZT trial is controversial to date. Should the drug have been approved? At the time, patients were pressuring the FDA for quicker approval and the FDA responded by adjusting the standards to meet their requests. This was done without much understanding of either the virus, the intervention, or the alternative trial design. There was no concept of an 'adaptive trial' at this stage—the trial was planned with a fixed design, only eventually accelerated, and adapted on the go. Concerns about patient recruitment and management strategies have been raised, such as the lack of coordination across twelve research centers that participated in the trial (Sonnabend 2011). There was a striking difference in mortality between the treatment and the control group (1 to 19 in the first 120 days) which decided in favor of expanding the treatment arm, but according to

Sonnabend, this discrepancy might have been an effect of biased patient selection and management. He also reports that the dose of initially administered AZT has been criticized for being too high. This might have led to beneficial short-term effects, but damaging long-term effects. Additionally, suspicions were raised about the practical limitations to blinding in such a study: The drug causes changes in routine blood counts that investigators need to see. Therefore we must conclude that investigators could know who was receiving AZT or placebo (Sonnabend 2011).

Doubts about the first AZT trial are primarily related to preference bias. Preference bias

> occurs when a research result unduly reflects the researchers' preference for it over other possible results. (…) It works (…) by increasing the likelihood of the preferred outcome rather than by bluntly fabricating it. (Wilholt 2009, 92)

It is not clear that this is what happened in the 1987 AZT trial, but if anything worrisome had happened, it seems to fall under the scope of preference bias. However, such subtle biasing is not attached to a particular design and it, unfortunately, permeates the landscape of biomedical and especially, pharmaceutical research (see Biddle 2007). Researchers, producers, policy makers, and patients had high hopes about AZT efficacy in absence of AIDS treatments. Everyone wanted the drug to work, and the trial was exceptional in both its urgent undertaking and its striking first outcomes.

Despite possible problems with the trial, the regulators had good reasons to approve the drug in face of reported evidence. Besides, pharmacovigilance, or monitoring for side effects of the drugs on the market, is in place to identify problems that might have been missed on the scale of pre-approval research. Time-spans of drug activity, effects after prolonged usage, and usage for different subgroups of patients can differ drastically. Benefits, side-effects, and long-term effects show at different times, and risk is inevitable: between waiting for the approval too long (denying people access to potentially effective therapy) and granting the approval too quickly (allowing for the provision of ineffective or harmful therapy). The balance was struck in the AZT case on the side of quick yet possibly unreliable assessment, although promising at the time, as opposed to waiting for more evidence in face of great public outcry. The therapy was made available, followed up, and finally, restricted in use. In addition to ethical considerations about research in exceptional circumstances, the AZT trial brought to attention patients' roles as advocates and partners in

healthcare decision-making. Today we find appeals to caution when it comes to such adaptations, but also tools and skills developed to plan and simulate a trial's course should adaptive interventions be made (Pallmann et al. 2018, 10-11). Special care needs to be taken to ascertain the best dosage, optimal sample size and representativeness, and comparators to the experimental treatment. Additional staff and resources need to be in place to reconcile the need to make interim analysis with the need to keep the results blinded. Local discrepancies between research centers should be minimized by transparent protocols and centralized oversight.

The second case has attracted philosophical attention both because of ethical challenges related to responses to emergencies and disasters (Calain 2016), but also because of a conjoined ethical-epistemic interest in innovative trial design (Upshur and Fuller 2016; Varghese 2021a, 2021b). In 2015 a phase III trial called 'Ebola ça Suffit!' ('Ebola, that's enough!') was conducted for testing recombinant vesicular stomatitis virus-Zaire Ebola vaccine (rVSV–ZEBOV) against Ebola virus disease. The design of the trial was not standard, due to time constraints, a limited amount of vaccine supplies, ethical concerns regarding the adoption of research methodology, and logistics and field operational challenges (Varghese 2021a, 2021b; Calain 2018). 'Ebola ça Suffit!' was a result of collective efforts to respond to the 2013-2016 West African Ebola epidemic that had caused the death of more than 11,000 people (Calain 2018). In August 2014, the Ebola epidemic was declared a public health emergency of international concern, and the World Health Organization (WHO) set up a panel of experts to consider ethical permissibility of testing potentially effective interventions for the disease in an accelerated manner. Within a few months, novel or repurposed therapeutic agents were tested for efficacy at various locations experiencing an outbreak.

The 'Ebola ça Suffit!' ring trial used cluster randomization instead of individually controlled randomization, and a delayed vaccination arm as the control group instead of a placebo control group, to mitigate the transmission of the disease in case of evidence of efficacy. Upon confirming a case of the Ebola virus, a ring (cluster) of all infected persons' contacts was established, as well as the contacts of their contacts (Henao-Restrepo et al. 2017). The clusters were assigned to either immediate vaccination or a delayed vaccination arm, allowing both groups to receive the vaccine, as opposed to treating the control group with a placebo. The randomization stopped after four months to allow the immediate provision of the vaccine to more adults, and to include younger age groups sooner (WHO 2015). The vaccine was approved for 'compassionate use' in outbreaks, meaning that it had been proven sufficiently safe and effective to be recommended, although it had not yet been formally approved by a

full regulatory process. According to later correspondence in *The Lancet*, the efficacy estimate of the vaccine remained at 100% despite concerns about bias in the research design (Longini et al. 2018; Metzger and Vivas-Martínez 2018). The vaccine eventually contributed to the suppression of the 2013-2016 Ebola virus disease epidemic (Geisbert 2017; Calain 2018).

Upshur and Fuller (2016) draw on the lessons from Ebola trials to call for a philosophy of clinical trials, asserting that the "inherent trade-off between ethical requirements and scientific rigor" is not resolved "necessarily through insisting on validity over ethics, but rather in reaching consensus on what is at stake" (2016, 11). They characterize the successful implementation of the ring vaccination strategy as "evidence that alternative trial designs can work", although they are not based on classical randomization which conventionally grants validity and reliability to clinical research. In a similar vein, Varghese (2021a, 2021b) uses the distinction between epistemic and non-epistemic values to argue that non-epistemic values were rightfully prioritized over epistemic values in the case of 'Ebola ca Suffit!' The urgency of the intervention was prioritized over scientific understanding that a standard procedure would advance. In a situation in which it was necessary to stop the virus from spreading, cluster randomization was considered good enough and prioritized over individual randomization. It is important to note that randomization was not altogether avoided. Like in the AZT case, it was only adapted. In the AZT trial, control arms were dropped only when beneficial results after initial randomization were observed, while in 'Ebola ca Suffit!' randomization was applied to clusters as opposed to individuals. Additionally, control groups were excised only with a delay, when beneficial effects of the vaccine were observed. Adaptation thus did not replace randomization and controlling, it rather complemented them and made the trial feasible and apt given the circumstances.

3. Towards Operational Exceptionalism

In a recent article, London and Kimmelman (2020) argue against what they call pandemic research exceptionalism, according to which situations of crisis justify lowering research standards. They identify three problematic assumptions which underpin research exceptionalism. The first is that any evidence, even if flawed, is preferable to more demanding studies whose benefits show later. In other words, that evidence generated by a faster method is preferred to evidence generated by a slower method. The second is that scientific rigor conflicts with care. The third problematic assumption is that researchers and sponsors are allowed to exercise discretion over the

organization and design of research in times of crisis. These assumptions, they contend, underlie alarming practices in pandemic research.

> The proliferation of small studies that are not part of an orchestrated trajectory of development is a recipe for generating false leads that threaten to divert already scarce resources toward ineffective practices, slow the uptake of effective interventions because of an inability to reliably detect smaller but clinically meaningful benefits, and engender treatment preferences that make patients and clinicians reluctant to participate in randomized trials. (London and Kimmelman 2020, 476)

The small studies referred to in this passage are numerous clinical trials that have been flourishing after the outbreak of the coronavirus epidemic, often investigating similar hypotheses in absence of coordinated oversight, rushing to publish results based on spurious correlations, and lacking adequate power to detect clinical benefit. Importantly, they are not a part of an "orchestrated trajectory of development", in other words, of a coordinated translational enterprise. When London and Kimmelman complain about "patients and clinicians being reluctant to participate in randomized trials", it is the adaptive randomized trials they refer to, which, according to them, hold a key to upholding both the standards of research excellence and time sensitivity.

> Sponsors, research consortia, and health agencies should prioritize research approaches that test multiple interventions, foster modularity, and permit timely adaptation. (…) Adaptive designs allow flagging interventions to be dropped quickly and promising alternatives to be added with fewer delays than would be incurred from the design and approval of new studies. (London and Kimmelman 2020, 477)

The argument is that adaptive trials should be undertaken under careful coordination in big research centers with the ability to conduct and analyze them, and not that any adaptation will satisfy. Quite the contrary—adaptation is here understood as a powerful, but demanding and complex method that can only work when five conditions of informativeness and social value are met, and under strict guidance and oversight.

The conditions identified by London and Kimmelman are importance, rigorous design, analytical integrity, complete, prompt, and consistent reporting, and feasibility. The condition of importance requires that trials address evidence gaps, aiming to detect effects that are "realistic but

clinically meaningful" (London and Kimmelman 2020, 476). An example of bad practice would be to concentrate resources on identical clinical hypotheses, creating competition for recruitment, and a neglect of other hypotheses, as was the case at the time of hydroxychloroquine hype when many trials were conducted in the US to test its efficacy for alleviating Covid-19 symptoms. Rigorous design is ascertained by randomization, blinding, controlling, and using meaningful endpoints. An example of bad practice would be "to forego a dummy comparator and use a nonvalidated surrogate endpoint" (London and Kimmelman 2020, 477). Analytical integrity means that designs should be "prespecified in protocols, prospectively registered, and analyzed in accordance with prespecification" (2020, 477). An example of bad practice would be preregistering a trial with a particular design while reporting the results that are generated by using a different design. Challenges connected to reporting primarily concern the preference for reporting only positive results, thereby withdrawing important information about negative results from clinicians and health systems. Another challenge is ascertaining quality control because expert reviewers are a scarce resource. The last condition, feasibility, is especially challenging in a crisis. London and Kimmelman argue that this nonetheless should not mean that it is justifiable to trade it off against the other four conditions. An increase in feasibility does not mean a decrease in addressing important evidence gaps, allowing less rigorous design, neglecting analytical integrity, or failing to transparently report. They give particular guidelines to clinicians:

> Individual clinicians should avoid off-label use of unvalidated interventions that might interfere with trial recruitment and resist the urge to carry out uncontrolled, open-label studies. They should instead seek out opportunities to join larger, carefully orchestrated protocols to increase the prospect that high-quality studies will be completed quickly and generate the information needed to advance individual and public health. Academic medical centers can facilitate such coordination by surveying the landscape of ongoing studies and establishing mechanisms for "prioritization review" to triage studies. (London and Kimmelman 2020, 477)

Channeling resources to orchestrated endeavors is a result of decades-long efforts to transform biomedical research towards better coordination and private-public partnerships, against the backdrop of the big data era that brought along the need to store, manage, and adequately use vast amounts of information and material. This portrays a picture in which the key to upholding standards for implementing adaptive design trials is in the hands of big research organizations with enough infrastructure and resources to

embark on such a complex task. I call this *operational exceptionalism*, in which centralization and coordination are the prerequisites for simultaneously increasing both the speed of generating evidence and the quality of this evidence. The only way to counter pandemic research exceptionalism seems to be by endorsing operational exceptionalism, according to which adaptive trials are not useful when run autonomously in local settings, but only when they are a part of larger projects based in selected research institutions.

4. Adaptive Trials and Precision Medicine

In this section, I focus on adaptive design as a clinical trial innovation that followed up on novel research methods and increased understanding of the intervention that is being assessed. In this cluster of cases, adaptive design trials are related to the rise of precision medicine.

Personalized or precision medicine[2] is an approach that tailors therapy to individual needs. It is often represented as 'P4' medicine: predictive, preventive, personalized, and participatory. The observations of highly variable drug responses have led to the development of a new scientific discipline from genetics, biochemistry, and pharmacology, namely pharmacogenetics, while advances in molecular medicine have led to a pharmacogenomics which seeks to understand the molecular mechanisms of drug response (Vogenberg, Barash, and Pursel 2010). In this new approach, patients' gene variations guide the selection and dosage of drugs. Several adaptive measures have been introduced to evaluate precision medicine treatments and to match the well-responding subgroups of patients with promising therapies, improve access, and evaluate efficacy earlier and more efficiently.

An example of an adaptive trial for a precision medicine intervention is the BATTLE-2 study—The Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination 2 (Garralda et al. 2019). Results generated in the 'adaptive phase' inform the randomization to different drugs or combinations based on mutation profiles.

[2] Terms 'personalized' and 'precision' medicine are often used interchangeably, although personalized medicine is the older term, while precision medicine is currently the preferred one, at least according to the US National Research Council (NRC). NRC adopts the following definition of both terms: "the tailoring of medical treatment to the individual characteristics of each patient (…) to classify to a specific treatment" (NRC 2011, 12). 'Precision medicine' is preferred to avoid the interpretation that 'personalized' means that each patient will be treated differently.

> Instead of using a fixed model—built on the training data only–adaptive strategies use the information on patients enrolled earlier in the testing set to continuously update the model and refine accrual throughout the entire study. (Garralda et al. 2019, 551)

Accrual design is a type of adaptive design—after the initial 'learning phase', in the 'adaptive phase' the ratio of patients randomly assigned to the experimental arm as opposed to the control arm changes to increase the proportion of patients in the arm that is performing better, which also increases the statistical power to detect clinical benefit (Garralda et al. 2019, 551). Adaptive enrichment is a term that refers to the modification of the patient eligibility criteria: if analysis shows that one subgroup has a more favorable response, the trial can be 'enriched' by modifying it to either exclusively or predominantly enroll patients from this subgroup (Thorlund et al. 2018). The seamless adaptive trial design allows for proceeding from phase II to phase III trial in a non-standard way. The results from the phase II trial are used to determine the initial patient allocation ratio, the planned total sample size (which can be rather smaller than the usual phase III samples that normally include from 300 to several thousand patients), and a potentially enriched set of patients, those that are thought to benefit the most from the intervention (Thorlund et al. 2018).

A significant part of the literature on adaptive trials, including guidelines for their implementation and reporting, comes from precision medicine research groups. They are raising problems related to their usage, but also providing means of addressing and overcoming them (for example, Garralda et al. 2019; Pallmann et al. 2018). Each trial is adapted in a particular way, so informed consent and the effective communication of risks and benefits to the patients can be a problem (Garralda et al. 2019, 552). Funders are suspicious about the validity of adaptive trials or lack experience in evaluating them, so may decide against approving them (Garralda et al. 2019; Pallmann et al. 2018). Regulators alike may be unfamiliar with adaptive design (Pallmann et al. 2018, 4). Operational challenges such as managing preplanned adaptations together with blinding may require additional staff and experience, as data may leak more easily and reach the sponsors, compromising the integrity of the trial (Pallmann et al. 2018, 5).

Overall, the efficacy of adaptive trials can be uncertain due to many factors, which are often local, contingent, and practical. Advocates of the usage of adaptive trials argue that these problems can be countered by transparent planning, careful execution, and the rigorous interpretation of the results. Additional skills in planning, conducting, and analyzing

adaptive design trials would need to be at hand, including statistical, mathematical, and modeling expertise. Since many clinicians are not trained in their usage, while the regulators are uncertain about their potential to avoid problems that the standard randomization and bias-reducing measures are in place for, their wider usage is both called for and cautioned against, sometimes by the very same authors (like Pallmann et al. 2018 from the clinical medicine side) and regulatory documents (FDA 2019). On the cautious side, it is emphasized that randomization and blinding remain the most reliable indicators of objectivity in clinical research and should not be bypassed in favor of shorter trials. A particularly problematic practice is reliance on non-randomized and non-blinded studies, and avoidance of control groups. On the affirmative side, novel designs such as multi-arm and seamless design trials are characterized as being a well-understood, ethical and efficient way of doing clinical research.

5. Adaptive Trials and the Productivity Crisis

From another vantage point, the pharmaceutical industry is voicing hopes about the usage of adaptive trials as a means to end the productivity crisis (Mahlich, Bartol, and Dheban 2021). In this section, I place the emergence of adaptive trials in a wider context of biomedical movements initiated to improve the productivity and cost-benefit of biomedical research.

Existing resources for the implementation of adaptive trials are a product of diverse measures in place to reform the pace and path by which biomedical innovations reach the market and patients. There is a consensus that pharmaceutical productivity has been going through a crisis for at least three decades (Munos 2009; Pammolli, Magazzini, and Riccaboni 2011; Taylor 2016). Advances in basic science resulting from stem cell research and the Human Genome Project (completed in 2003) have not resulted in clinical applications as quickly as was initially expected (Solomon 2015, 161-163). The so-called 'pipeline problem' refers to the slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients (FDA 2004), and what has thus been sought is the 'uncorking of the bottleneck' of pharmaceutical innovation. Furthermore, it has been estimated that it takes 17 years on average for research results to find implementation in clinical practice, which has been considered too slow (Morris et al. 2011). These problems have motivated different initiatives to transform the way biomedical research is conducted. Consequently, in the 2000s the idea of 'translational research' became a "buzzword" (Fishburn 2013, 487), a "mantra" (Maienschein et al. 2008, 43), "in vogue"

(Fang and Casadevall 2010, 563), and even "an imperative" (Harrington and Hauskeller 2014).

The translational approach is based on the prospect of directly matching ideas for new therapies with the needs of patients observed in the clinic. It can be described as a cluster of accelerated transitions in the development of a medical product at the intersection of basic and clinical research, and more broadly, the intersection of prevention, guidelines, and health policy. These transitions are mostly accelerated by external, non-scientific measures: better communication between researchers from different disciplines, better communication between different stakeholders such as patients, researchers, regulators, and producers of therapies, interdisciplinary training, collection of databanks, and building of new research centers that would facilitate the interaction between basic and clinical research. Most of the philosophical work on translational medicine shares the view that it is hard to "find substance amidst the rhetoric" and that the movement "appears to offer no more than a metaphor" (Fuller 2016).

Robinson (2019) pointedly argues that attempts to find epistemic novelty in the new medical movements fail because their objectives are better assessed by a social epistemology approach attentive to market forces and financialized models of science and innovation.

> TrM (translational medicine) cannot be analyzed merely in terms of its epistemic novelty. After all, it has relocated research practices from the R&D departments of biopharmaceutical partners to university laboratories. (…) It is—in its current functionality—a structural configuration for the externalization of the costs and risks of early-stage biopharmaceutical research and development onto universities. (Robinson 2019, 4404)

Translational initiatives are thus comprised of "questions, methods, areas of concern, and projects" which are "a product of a specific set of financial, commercial and industry-driven shifts" (Robinson 2019, 4404).

Justification in terms of patient empowerment and acceleration of discovery and research is shared in both translational and precision initiatives. Both movements value speed in discovery, research, and development, which is not only a success of science but of a larger cooperative work and exchange of many stakeholders, institutions, and disciplinary cultures. Finally, it was the biobanks collected as part of translational initiatives in the early 2000s that have made it possible to

personalize medicine in the 2010s.[3] Contemporary translations are very likely to occur on the terrain of precision medicine and they occur there faster due to changes in drug discovery methods and clinical assessment routes.[4] In drug discovery, methods such as high-throughput screening can identify molecular targets among a vast number of potential matches (Adam 2011), and in clinical assessment, the adaptive design facilitates matching subgroups of patients with promising therapies based on genetic profiling.

Against this backdrop, the emergence and development of adaptive designs can be traced to translational and precision medicine centers. Increased awareness of the need for trained statisticians, mathematicians, and big-data experts in clinical research teams, and opening up to interdisciplinarity in a variety of contexts where singular expertise is not sufficient, have contributed to the fact that adaptive trials are nowadays planned, conducted, analyzed, and regulated with more understanding and expertise. However, this fact alone does not grant justification for their usage in every instance of clinical research. Clear rationale, transparent protocols, and importantly, operational conditions, need to be in place. It seems that especially operational conditions cannot be satisfied on smaller scales of individual clinics and local research centers, but rather "orchestrated" by big consortia with sufficient resources and in close cooperation with policy makers and industrial partners. The complexities that this operational exceptionalism brings in a value-laden and interest-driven environment of biomedical research are beyond the scope of this paper but call for attention and discussion by philosophers and social scientists alike.

6. Conclusion

The success of Covid-19 adaptive trials is not a consequence of research exceptionalism or lucky guesses, but of prior experience in healthcare crisis-management and structured efforts to reform biomedical research and innovation. That said, it is important to qualify the context in which adaptive trials are conducted and implemented. It is a private-public partnership of many stakeholders, highly burdened with both social commitments and commercial interests. Importantly, the apparent flexibility of adaptive trials is not as flexible as it may seem at first sight.

[3] Initiatives such as the NIH Roadmap in the US (NIH 2014) and the reforms outlined in the Cooksey Report (2006) in the UK.

[4] In 2017 the number of FDA approvals hit a two-decade high with 46 novel medicines, followed by 59 approvals in 2018 (Mullard 2019). More precision medicines and tests were approved in 2017 than any year before (Bilkey et al. 2019), many of them based on biomarkers reliant on genetic testing.

They require both planning and rigor to be successful, just as much as fixed trials. The usual standards of rigor remain unchallenged in the new context, coming down to blinding, randomization, and controls. A new and most valuable element of their success is their speed. However, it is a qualified speed that, rather than trading off against reliability, requires reliability to achieve epistemic benefit. Daniel Steel (2010, 26-28) would call it an extrinsically epistemic value, i.e. a value that is not truth conducive *per se* but in combination with an intrinsically epistemic value like accuracy. Adaptive designs ground their reliability in "orchestration" and integration of different evidence and expertise. In the case of clinical trials, the benefits are both ethical—earlier access to therapies, and epistemological—earlier results that inform policies and further research. Still, adaptive design trials require additional resources and coordination, which is the most pressing practical obstacle to their wider, local implementation. They have been increasingly developed as a part of the precision medicine approach, and have recently been used to assess Covid-19 therapies. It is important to keep in mind though, that this does not grant them the status of the new standard. It means at best that the standard welcomes necessary upgrades and contextual adjustments.

Acknowledgments

I would like to thank two anonymous reviewers for their extremely helpful comments and suggestions, and Lucie White for her detailed feedback on the revised version of the paper.

REFERENCES

Berry, Donald A. 2011. "Adaptive Clinical Trials: The Promise and the Caution." *Journal of Clinical Oncology* 29 (6): 606–9. https://doi.org/10.1200/JCO.2010.32.2685.

Biddle, Justin. 2007. "Lessons from the Vioxx Debacle: What the Privatization of Science Can Teach Us about Social Epistemology." *Social Epistemology* 21 (1): 21–39. https://doi.org/10.1080/02691720601125472.

Bilkey, Gemma A., Belinda L. Burns, Emily P. Coles, Trinity Mahede, Gareth Baynam, and Kristen J. Nowak. 2019. "Optimizing Precision Medicine for Public Health." *Frontiers in Public Health* 7: 42. https://doi.org/10.3389/fpubh.2019.00042.

Branch-Elliman, Westyn, A Rani Elwy, and Paul Monach. 2020. "Bringing New Meaning to the Term 'Adaptive Trial': Challenges of Conducting Clinical Research during the Coronavirus Disease

2019 Pandemic and Implications for Implementation Science." *Open Forum Infectious Diseases* 7 (11). https://doi.org/10.1093/ofid/ofaa490.

Calain, Philippe. 2018. "The Ebola Clinical Trials: A Precedent for Research Ethics in Disasters." *Journal of Medical Ethics* 44 (1): 3–8. https://doi.org/10.1136/medethics-2016-103474.

Cooksey, Sir David. 2006. *A review of UK health research funding.* London: Crown, HM Treasury. Accessed November 12, 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/228984/0118404881.pdf

Crewe, Tom. 2018. 'Here was a plague. Review of the books *How to Survive a Plague: The Story of How Activists and Scientists Tamed Aids, Patient Zero and the Making of the Aids Epidemic*, *Modern Nature: The Journals of Derek Jarman, 1989–90*, *Smiling in Slow Motion: The Journals of Derek Jarman, 1991–94* and *The Ward*'. *London Review of Books* 40 (18): 7–16. Accessed September 3, 2021. https://www.lrb.co.uk/the-paper/v40/n18/tom-crewe/here-was-a-plague

Epstein, Steven. 1996. *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Reprint. Medicine and Society 7. Berkeley, Calif.: University of California Press.

European Medicines Agency (EMA). 2017. *Adaptive pathways.* Accessed November 12, 2021. https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways

Fang, Ferric C., and Arturo Casadevall. 2010. "Lost in Translation—Basic Science in the Era of Translational Research." *Infection and Immunity* 78 (2): 563–66. https://doi.org/10.1128/IAI.01318-09.

Fishburn, C. Simone. 2013. "Translational Research: The Changing Landscape of Drug Discovery." *Drug Discovery Today* 18 (9–10): 487–94. https://doi.org/10.1016/j.drudis.2012.12.002.

Food and Drug Agency (FDA). 2004. *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*. Accessed September 3, 2021. https://www.who.int/intellectualproperty/documents/en/FDAproposals.pdf

Food and Drug Agency (FDA). 2019. *Adaptive Design Clinical Trials for Drugs and Biologics. Guidance for Industry*. Accessed November 12, 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry

Fuller, Jonathan. 2016. "The Reading Room: 'Making Medical Knowledge'". *British Medical Journal* blogs. Accessed November 12, 2021.

https://blogs.bmj.com/medical-humanities/2016/04/25/the-reading-room-making-medical-knowledge/

Garralda, Elena, Rodrigo Dienstmann, Alejandro Piris-Giménez, Irene Braña, Jordi Rodon, and Josep Tabernero. 2019. "New Clinical Trial Designs in the Era of Precision Medicine." *Molecular Oncology* 13 (3): 549–57. https://doi.org/10.1002/1878-0261.12465.

Geisbert, Thomas W. 2017. "First Ebola Virus Vaccine to Protect Human Beings?" *The Lancet* 389 (10068): 479–80. https://doi.org/10.1016/S0140-6736(16)32618-6.

Harrington, Jean, and Christine Hauskeller. 2014. "Translational Research: An Imperative Shaping the Spaces in Biomedicine." *Tecnoscienza: Italian Journal of Science & Technology Studies* 5 (1): 191–202.

Henao-Restrepo, Ana Maria, Anton Camacho, Ira M. Longini, Conall H. Watson, W. John Edmunds, Matthias Egger, Miles W. Carroll, et al. 2017. "Efficacy and Effectiveness of an RVSV-Vectored Vaccine in Preventing Ebola Virus Disease: Final Results from the Guinea Ring Vaccination, Open-Label, Cluster-Randomised Trial (Ebola Ça Suffit!)." *The Lancet* 389 (10068): 505–18. https://doi.org/10.1016/S0140-6736(16)32621-6.

London, Alex John, and Jonathan Kimmelman. 2020. "Against Pandemic Research Exceptionalism." *Science* 368 (6490): 476–77. https://doi.org/10.1126/science.abc1731.

Longini, Ira M., John-Arne Røttingen, Marie Paule Kieny, W. John Edmunds, and Ana Maria Henao-Restrepo. 2018. "Questionable Efficacy of the RVSV-ZEBOV Ebola Vaccine – Authors' Reply." *The Lancet* 391 (10125): 1021–22. https://doi.org/10.1016/S0140-6736(18)30559-2.

Mahlich, Jörg, Arne Bartol, and Srirangan Dheban. 2021. "Can Adaptive Clinical Trials Help to Solve the Productivity Crisis of the Pharmaceutical Industry? - A Scenario Analysis." *Health Economics Review* 11 (1): 4. https://doi.org/10.1186/s13561-021-00302-6.

Maienschein, Jane, Mary Sunderland, Rachel A. Ankeny, and Jason Scott Robert. 2008. "The Ethos and Ethics of Translational Research." *The American Journal of Bioethics* 8 (3): 43–51. https://doi.org/10.1080/15265160802109314.

Matthias, Adam. 2011. "Multi-Level Complexities in Technological Development: Competing Strategies for Drug Discovery." In *Science in the Context of Application*, edited by Martin Carrier and Alfred Nordmann, 274:67–83. Boston Studies in the Philosophy of Science. Dordrecht: Springer Netherlands. https://doi.org/10.1007/978-90-481-9051-5.

Metzger, Wolfram G., and Sarai Vivas-Martínez. 2018. "Questionable Efficacy of the RVSV-ZEBOV Ebola Vaccine." *The Lancet* 391 (10125): 1021. https://doi.org/10.1016/S0140-6736(18)30560-9.

Morris, Zoë Slote, Steven Wooding, and Jonathan Grant. 2011. "The Answer Is 17 Years, What Is the Question: Understanding Time Lags in Translational Research." *Journal of the Royal Society of Medicine* 104 (12): 510–20. https://doi.org/10.1258/jrsm.2011.110180.

Mullard, Asher. 2019. "2018 FDA Drug Approvals." *Nature Reviews Drug Discovery* 18 (2): 85–89. https://doi.org/10.1038/d41573-019-00014-x.

Munos, Bernard. 2009. "Lessons from 60 Years of Pharmaceutical Innovation." *Nature Reviews Drug Discovery* 8 (12): 959–68. https://doi.org/10.1038/nrd2961.

National Institute of Health (NIH). 2014. *A Decade of Discovery: The NIH Roadmap and Common Fund (2004-2014).* Accessed November 12, 2021. https://commonfund.nih.gov/sites/default/files/ADecadeofDiscoveryNIHRoadmapCF.pdf

National Research Council (U.S.). 2011. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. Washington, D.C: National Academies Press.

Pallmann, Philip, Alun W. Bedding, Babak Choodari-Oskooei, Munyaradzi Dimairo, Laura Flight, Lisa V. Hampson, Jane Holmes, et al. 2018. "Adaptive Designs in Clinical Trials: Why Use Them, and How to Run and Report Them." *BMC Medicine* 16 (1): 29. https://doi.org/10.1186/s12916-018-1017-7.

Pammolli, Fabio, Laura Magazzini, and Massimo Riccaboni. 2011. "The Productivity Crisis in Pharmaceutical R&D." *Nature Reviews Drug Discovery* 10 (6): 428–38. https://doi.org/10.1038/nrd3405.

Riley, William T. 2016. "Chapter 18 - a New Era of Clinical Research Methods in a Data-Rich Environment." In *Oncology Informatics*, edited by Bradford W. Hesse, David K. Ahern, and Ellen Beckjord, 343–55. Boston: Academic Press. https://doi.org/10.1016/B978-0-12-802115-6.00018-5.

Robinson, Mark D. 2019. "Financializing Epistemic Norms in Contemporary Biomedical Innovation." *Synthese* 196 (11): 4391–4407. https://doi.org/10.1007/s11229-018-1704-0.

Solomon, Miriam. 2015. *Making Medical Knowledge*. Oxford: Oxford University Press. https://doi.org/10.1093/acprof:oso/9780198732617.001.0001.

Sonnabend, Jospeh. 2011. 'Remembering the Original AZT Trial'. POZ Magazine Online. Accessed November 12 2021. https://www.poz.com/blog/-v-behaviorurldefaul

Stallard, Nigel, Lisa Hampson, Norbert Benda, Werner Brannath, Thomas Burnett, Tim Friede, Peter K. Kimani, et al. 2020. "Efficient Adaptive Designs for Clinical Trials of Interventions for Covid-19." *Statistics in Biopharmaceutical Research* 12 (4): 483–97. https://doi.org/10.1080/19466315.2020.1790415.

Steel, Daniel. 2010. "Epistemic Values and the Argument from Inductive Risk." *Philosophy of Science* 77 (1): 14–34. https://doi.org/10.1086/650206.

Taylor, David. 2015. "The Pharmaceutical Industry and the Future of Drug Development." In *Pharmaceuticals in the Environment*, edited by Ronald E. Hester and Roy M. Harrison, 1–33. The Royal Society of Chemistry. https://doi.org/10.1039/9781782622345-00001.

Thorlund, Kristian, Jonas Haggstrom, Jay JH Park, and Edward J. Mills. 2018. "Key Design Considerations for Adaptive Clinical Trials: A Primer for Clinicians." *BMJ* 360: k698. https://doi.org/10.1136/bmj.k698.

Upshur, Ross, and Jonathan Fuller. 2016. "Randomized Controlled Trials in the West African Ebola Virus Outbreak." *Clinical Trials* 13 (1): 10–12. https://doi.org/10.1177/1740774515617754.

Varghese, Joby. 2021a. "Influence and Prioritization of Non-Epistemic Values in Clinical Trial Designs: A Study of Ebola Ça Suffit Trial." *Synthese* 198 (10): 2393–2409. https://doi.org/10.1007/s11229-018-01912-0.

———. 2021b. "Non-Epistemic Values in Shaping the Parameters for Evaluating the Effectiveness of Candidate Vaccines: The Case of an Ebola Vaccine Trial." *History and Philosophy of the Life Sciences* 43 (2): 1–15. https://doi.org/10.1007/s40656-021-00417-3.

Vogenberg, F. Randy, Carol Isaacson Barash, and Michael Pursel. 2010. "Personalized Medicine." *Pharmacy and Therapeutics* 35 (10): 560–76.

Wilholt, Torsten. 2009. "Bias and Values in Scientific Research." *Studies in History and Philosophy of Science Part A* 40 (1): 92–101. https://doi.org/10.1016/j.shpsa.2008.12.005.

World Health Organization (WHO). 2015. 'Ring Vaccination Trial Consortium Ebola ça Suffit! Ebola vaccine Phase 3 trial Guinea'. Accessed September 3, 2021. http://www.who.int/immunization/research/meetings_workshops/3_Ebola_Ring_vaccination_Phase_3_trial_2015.pdf