

Title: Adaptive Trials for Tuberculosis: Early Reflections on Theory and Practice

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SUMMARY

Setting: Adaptive designs (ADs) have been proposed for tuberculosis (TB) treatment trials. This call for innovation occurs against the backdrop of fundamental changes in the acceptable evidence base in TB treatment.

Objective: To contextualize ADs for TB and explore early responses from those working in the field.

Design: A qualitative study investigating processes of theoretical and practical change in randomized controlled trials. As part of this study, twenty-four interviews were conducted with professionals involved in AD trials, half of whom worked in the TB field.

Results: Clinical trialists working on AD trials in TB are positive about the efficiencies these designs offer, but remain cautious about their suitability. In addition to technical concerns, informants discussed the challenges of implementing AD in developing countries, including limited regulatory capacity to evaluate proposals; investments needed in infrastructure and site capacity; and challenges of informed consent. Respondents identified funding, interdisciplinary communication and regulatory and policy responses as additional concerns potentially affecting the success of AD for TB.

Conclusion: Empirical research is needed into patient experiences of AD, including informed consent. Further consideration is needed of the contexts of innovation in trial design. These are fundamental to the successful translation of theory into practice.

Keywords: Adaptive design; clinical trials; tuberculosis; statistics; context

INTRODUCTION

The testing of new regimens for drug sensitive and drug resistant tuberculosis (TB) is undergoing a paradigm shift. After decades of stagnation in which no new drugs were approved, the TB field has seen rapid progress, with the recent approval of two new drugs ¹ and a considerable number of new candidates in the pipeline ². While the conventional pathway of drug testing persists, alternative routes are challenging the notion of the large scale, standalone confirmatory phase III trial as the gateway to drug approval, recommendation and use. For example, the FDA and EMA conditional approvals of Bedaquiline and Delamanid on the basis of phase II data using surrogate endpoints has called into question the kind of evidence needed for policy recommendations ³. Likewise, the partial roll-out of the 'Bangladesh regimen' on the basis of results seen in observational studies ⁴⁻⁶, prior to the findings of an ongoing phase III trial ⁷, challenge the status of what has traditionally been seen as the gold standard in medical research.

Against this backdrop, there have been calls for greater flexibility and speed in TB treatment research ¹, and more specifically for the use of adaptive designs (ADs) ⁸⁻¹⁰. ADs allow investigators to make pre-planned changes to a trial on the basis of accruing information while the trial is ongoing. This could be in relation to the number of treatment arms, the randomization schedule, or even outcome measures. Extensively elaborated in theoretical terms since the 1950s ¹¹, they have been slow to be adopted in practice ¹², and have only recently been discussed in the TB community. The chief selling point of ADs is that they are more efficient than traditional trials, potentially allowing investigators to answer multiple questions in a shorter timeframe using fewer patients (with the obvious cost savings this implies).

While there has been extremely limited experience with ADs in TB, the barriers and opportunities they present have been broadly described elsewhere ¹³⁻¹⁶. As already mentioned, time and cost savings are chief amongst the benefits. Among the challenges is a lack of clarity about the definition of ADs and what regulators

and reviewers consider acceptable adaptations¹; public funding structures that are ill-suited to the flexibility required by e.g. indeterminate sample sizes; the length of time and additional resources needed to design studies using complex simulation methods; structure and role of data safety monitoring boards, who are required to make key design decisions on an ongoing basis; information leakage following repeated interim analyses; and difficulties interpreting the results of AD trials. The message from the literature is that barriers to the uptake of ADs are logistical and regulatory rather than statistical.

In the TB field, ADs have been proposed as a solution to the question of how to select the most promising regimens for testing in phase III, given the number of options now available. The Multi Arm Multi Stage (MAMS) design, originally developed in oncology, has been advocated by Phillips et al ⁸ and adopted by the Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics (PanACEA). With a MAMS design, multiple regimens can be tested simultaneously against a common control, with poorly performing arms dropped at planned interims during the trial. The PanACEA MAMS-TB-01 trial reported its results in 2015 and concluded that ADs were “feasible for multi-centre TB clinical trials and could speed regimen development” ¹⁷. Other consortia are following suit; for example, TRUNCATE TB uses a MAMS design and the TB-Practecal trial has also adopted an adaptive selection design, while the END-TB trial, currently in development, will use adaptive randomization. In XDR-TB, the TB Alliance’s NiX-TB trial uses an adaptive design, allowing the addition of new treatments over the course of the study, based on accumulating information.

To date, the literature on the use of ADs in the TB field has been theoretical, focusing on statistical issues, such as simulation methods, selection of minimum treatment effect, control of type 1 error, and choice of endpoints, including surrogate endpoints ^{8,9,18}. Empirical research is absent on the challenges facing investigators in practice, as they design and implement such studies. In this

¹ FDA draft guidance issued in 2010 distinguished between ‘well understood’ and ‘less well understood’ adaptations.

paper, we address this gap by presenting findings from a qualitative study of methodological change in relation to the randomized controlled trial (RCT).

METHODS

Data for this paper are drawn from a broader study investigating processes of theoretical and practical change in RCTs, focusing on AD. The research sought to understand the translation of RCT methodology between theory and practice and between differently resourced settings. The study consisted of two parts: one exploring perspectives on methodological innovation among clinical trialists, and one exploring the practical implementation of an adaptively designed TB trial among researchers, research participants and community members. Forty-eight interviews and two focus groups were conducted in total: twenty-four interviews with trialists involved in theoretical work on AD; twenty-four interviews with staff and patients taking part in an adaptively designed TB treatment trial in Tanzania; and two focus groups with community representatives in Tanzania.

In this paper, we focus on the data collected from key informants working on adaptively designed trials in the TB field. Findings from patients and community members will be published separately. The key informants totaled twelve and included academic statisticians, clinician investigators, project managers, pharmacologists and software developers. Five were principal investigators (PIs) or co-PIs on adaptively designed TB trials in the planning or implementation stages and they represented five countries between them: the United Kingdom, the Netherlands, Germany, Tanzania and the United States. Sampling initially involved the selection of gateway informants working on adaptively designed TB trials, who would be able to identify others working in this small field. Thereafter, snowballing was used to identify additional informants, selected on the basis of their expertise and ability to provide rich accounts for in-depth study ^{19, 20}. While the broader research relied on a larger

sample, we follow Guest et al ²¹ in finding a sample of 12 adequate to answer the narrow question addressed in this paper.

Semi-structured interviews were conducted by the author, digitally recorded and subsequently transcribed. The topics discussed included rationales for research design choices in TB clinical trials; challenges and achievements in gaining acceptance for AD among colleagues; changing trial team dynamics; the practicalities of implementing AD trials; and patient/community considerations in using AD in TB. Key informants were not provided with a standard definition of AD, since a key question for this research was how concepts travel and change over time, between disease areas, and across different locations.

All participants provided written informed consent prior to being interviewed. Data were imported into NVivo 10 software for qualitative data analysis and coded inductively to identify key issues of concern to informants. The thematic analysis proceeded iteratively, until no new themes were identified in the data. Ethics approval for this study was granted by the Amsterdam Institute for Social Science Research Ethical Advisory Board in the Netherlands. In Tanzania, it was approved by the National Institute for Medical Research and the local IRB.

FINDINGS

The findings of this research concern the importance of context for statistical innovations in trial design. Whereas the methodological literature focuses on statistics from a theoretical point of view, our informants underscored the lively and little-documented world of statistics-in-practice in TB clinical trials. Context, as articulated by them, relates to the appropriateness of particular methods for particular diseases, locations, and evidentiary demands. We discuss each of these in turn below.

Appropriateness of adaptive designs for Tuberculosis

"[Y]ou have to put the statistical methodology to work in its context, and if it's a bit divorced from its context, it's not going to have significant benefits. And there might be some things, designs that would be sensible in oncology, which don't make sense to us in TB" (KI021, Clinician)

One of the first questions that informants raised was the transferability of ADs, both between the private and the public sector, and between disease areas. The latter was a particular concern for those working on TB, as the above quotation illustrates. In general, there was a sense of ambivalence about these innovations: the easy appeal of generic benefits was offset against the specific challenges posed by TB. The allure of ADs was framed first and foremost as a response to the failure of the traditional testing approach; as one clinician put it when asked about the rationale for ADs in TB:

"[It's] the impulse that we just have to try and do drug development better. Especially after the moxifloxacin debacle. You know, we just spent, as a community, ten years evaluating a regimen that isn't capable of delivering a four-month duration of treatment. What did we do wrong?" (KI021, Clinician)

Added to this was an awareness of a changing evidentiary environment. The approval of Bedaquiline and Delamanid on the basis of limited phase II data and surrogate endpoints left some feeling skeptical about the way in which clinical trial evidence is interpreted and put into policy and practice. Furthermore, the very basis of the large confirmatory phase III trial as a prerequisite for the rollout of new treatment regimens was also being undermined by the adoption of the 9-month 'Bangladesh regimen' for multidrug resistant tuberculosis prior to the results of the pivotal phase III 'STREAM' trial.

"There are people out there who are saying 'do we need to do STREAM?' and indeed the Union itself, strangely, is actually encouraging some of these cohort studies at the same time as STREAM. Now you could say, that's OK

providing at the end of the day, if STREAM comes up and says it's not quite as good as we thought it was, it's important to recognise that. But scientific opinion as to what people should do is a very strange thing; sometimes it's not always based on good evidence and people have their own ideas." (KI02, Statistician)

"So they're rolling it [the Bangladesh regimen] out in a pretty gung-ho kind of way... and as a statistician you might look at it and be a little dubious about some of what's going on." (KI016, Statistician)

Together, these changes in the evidentiary landscape for TB treatment provided a new, albeit cautious, receptiveness to innovations in trial design, particularly those where the boundary between learning and confirming was less sharply drawn. For instance, whereas 'learning' only happens traditionally in early phase trials, some ADs are based on the concept of continuous learning during the course of a trial, even in the confirmatory phase.

By contrast, various rationales for AD were identified. Selection designs were said to provide a means to choose the most promising regimens to take forward to phase III in an environment of many new candidates. Informants also suggested that ADs move beyond an adherence to the notion that there should be a single standard regimen for a limited number of subsets of the disease. Instead, they are commensurate with the search for multiple effective regimens, with the goal of stemming resistance. Finally, and most commonly mentioned, was the idea that ADs are more efficient, in terms of the number of patients required, because of, for example, the use of a common control group and the ability to drop poorly performing arms. As a result, they are more cost-effective, which informants felt was a key advantage in the poorly-resourced field of TB drug development.

While those who were interviewed for this study were already involved in ADs for TB, they nonetheless remained critical of potential innovations. The main concern was the suitability of ADs for TB given the length of time to events and

the ability of surrogate endpoints to predict long-term efficacy. As various informants pointed out, even on liquid media, a negative is not considered definitive until 42 days after the start of incubation; add to this the time needed for data entry and cleaning and it may be eleven weeks after the start of treatment before the early response information is available. As one PI pointed out, *"that doesn't seem all that early in the context of a 39 week experimental regimen"* (KI023, Epidemiologist). Echoing this, and summing up a common sentiment among informants, another statistician observed:

"I think there are some of those issues where perhaps we're forcing this trial design (MAMS) into the TB world, when in fact perhaps there are some tools that the TB world doesn't have to be able to implement those correctly, including not being able to know exactly at two months whether the person's failed or not because it takes a longer time for the lab to get the results back." (KI016, Statistician)

Challenges implementing adaptive designs in resource-limited settings

A key aim of this research was to investigate how methods travel. In addition to travel between disease areas (discussed above), it looked at travel between differently resourced settings. Much of the experience with ADs has been gained in oncology in well-equipped clinical environments, funded by the pharmaceutical industry and underpinned by sophisticated regulatory machinery. Only relatively recently has there been talk of using these designs in the field of global health to improve disease management studies in some of the poorest parts of the world ²². Informants in this study were split on the ease of implementing ADs in developing countries. While none felt the challenges were insurmountable, there was disagreement as to their significance. The three central concerns were i) regulatory capacity to evaluate ADs ii) infrastructure and site capacity and iii) informed consent. We look at each of these in turn below.

i) Regulatory capacity to evaluate adaptive designs

Across the board, informants were inclined to think that the regulatory agencies in the places where TB trials would be conducted would not have sufficient knowledge or experience of ADs to be able to evaluate proposals adequately.

"I suspect that the capability of evaluating the risks and benefits of those designs is not strong in reality...they might not be able to engage with it with sufficient scrutiny to really identify the key issues." (KI021, Clinician)

Indeed, this was borne out in practice by one trial, whose design passed unqueried:

"I: In terms of the regulatory authorities, has this design elicited any particular response, any particular difficulties?

R: No, I think it hasn't. And we expected some. We got completely other questions... we expected difficult questions on the design and we were surprised we didn't get any...So we thought actually they didn't understand the design." (KI005, Project Manager)

Some were concerned that regulators would take a conservative position in relation to anything new, and several suggested trialists engage regulators in a process of education on design innovations.

ii) Infrastructure and site capacity

While there was consensus that conducting TB trials required investment in site infrastructure and scientific capacity building, views differed as to whether this was increased in the case of ADs. For some, the designs were no more complex than standard trials in terms of implementation, and indeed had the potential to reduce complexity for sites, as the following informant suggests:

"I think what people envisioned...was complete chaos at the sites. That how were the sites going to be able to put together the regimens for the adaptive design? How are you going to ensure that the adaptation was translated or transferred to all the sites, especially in a multi-site study? ... But there is enormous complexity already in the sites in treating MDR-TB. They're generally managing formularies of ten, twelve, fifteen drugs, and individual clinicians are having to come up with regimens and pharmacists are having to respond to those individualized regimens and changes in regimens, as well as stock-outs and the other things that happen that are out of their control. So... they already manage an enormous amount of complexity and if anything, this will actually reduce the complexity, because there are a limited number of drugs" (KI023, Epidemiologist)

This was a minority view, however, and more often than not, respondents felt that ADs increased complexity in a variety of ways, particularly when the number of treatment arms was increased. These related to study drug management (supply, packaging, labeling, shipping, storing); timeliness of data entry and cleaning; and responsiveness of the trial management group. The question of how to get data in a timely fashion was felt to be critical, since it had a direct impact on the ability to make adaptations. Electronic source was proposed as one solution to this, with at least one trial having used this successfully. E-source requires internet connectivity, which at one site meant installing a satellite dish; even then, challenges remained:

"We had problems in this study where tablets didn't fully connect and we had issues...with sites having the wrong version of source. Now, they wouldn't work, they wouldn't open, so they weren't filling out the wrong version; they simply had errors when they tried to open up an old version of form number 1; they couldn't open it because they didn't have the new version. We were able to fix it and it wasn't ever a threat to the integrity of the data, but it did create a problem for some of the sites some of the time." (KI020, Software Developer)

In spite of this, e-source was viewed as a positive innovation, facilitating remote monitoring, increasing the speed and accuracy of data transfer, and eliminating the problems associated with paper CRFs, such as long-term secure storage.

iii) Informed Consent

How to consent patients in adaptive trials was an area where informants felt there was a lack of experience or research on which to draw, whether in resource limited settings or not. Questions such as whether patients need to be informed about the adaptive nature of the design or not, and whether and how to re-consent patients following an adaptation were unresolved. For some, explaining the adaptive nature of the design presented an additional hurdle in an already difficult process of patient communication. These informants felt that existing concepts, such as randomization, were already poorly understood and that in many cases, patients failed to appreciate they were taking part in research at all. By contrast, others thought the adaptive message was an intuitive one, along the lines of ‘we’re going to try out this medicine and if it seems not to work, we’ll switch to another one’. Particularly in relation to MDR-TB, this was seen as a message that patients would find easy to understand. The two poles of opinion on informed consent in adaptive trials are illustrated in the following excerpts:

"So when you're starting to talk about, we're gonna randomize you to a regimen, you won't know which one it is, I won't know which one it is, and it's possible actually we might stop you and put you on another regimen during the trial – it does become very complicated. So the question of how you communicate the idea – because you're saying "we don't know which regimen you're on, but it's possible somebody else will tell us that actually it isn't the right regimen for you and we should stop it or change it" – then you have to get into explaining the whole structure of how the management of a trial works! And that's a big...to explain that in concepts that people can

really grasp and understand the implications for them, I think is not trivial."
(KI021, Clinician)

"Sometimes perhaps we assume too much that people in developing countries find it more difficult to understand than people in the technically advanced countries. It's not necessarily the case... And it doesn't have to be a sophisticated explanation, but just to say, look, maybe in the context of adaptive design, there may be a point in time at which we feel one treatment is not working so well, in which case we won't keep on treating with that one, but there may be others we can bring in. I don't think it should be that much more difficult, I don't think it requires a university education before you can join the trial!" (KI02, Statistician)

Beyond questions of individual informed consent, the extent of communication following interim analyses remained a question, in terms of how much the wider community should be informed. Dropping arms mid-trial has the potential to damage the reputation of a study if the reasons for this are not properly communicated. For example, rather than being seen as an integral part of the research process, it may be seen as a research failure and discourage others from taking part. One trialist conveyed this concern as follows:

"We are emphasizing that these arms were not stopped because they were unsafe or posing a risk to patients, but they were stopped because we were quite confident they would not lead to a significant improvement over the standard of care. So this is inherent in the design and that's why it was quite an important message that we try to convey. I'm not sure in how far actually this fact has reached the local community." (KI011, Clinician)

In summary, the challenges of implementing ADs in resource-limited settings should not be seen as unique to the TB context, but as part of a much wider

discussion about innovations in trial design. A number of other issues were raised, which we discuss below.

Funding, research and policy cultures

Amongst the other issues to have an impact on the success of ADs for TB, respondents identified funding, interdisciplinary communication and regulatory and policy responses as key concerns. We discuss each in turn below.

Funding

ADs, by nature, require flexibility. Informants were quick to observe that funding structures do not readily accommodate such flexibility, which may concern the number of arms in the trial, the number of patients, and the length of the trial.

"The MAMS thing, it's very difficult to actually say to the funder, we know how much this trial will cost, because we don't know which arms will be stopped" (KI02, Statistician)

"Basically you're starting the trial and you don't know with how many patients you'll end up. So that's a financial thing - contracts with the sites, and also the funding agency doesn't really know how many patients they will eventually have to fund and they would need to allow flexibility in the budget." (KI011, Clinician)

Not only were funders seen as a potential barrier to ADs, but equally senior managers, who might be reluctant to return funds should a trial end early. 'How to fail faster', an oft-heard mantra in AD advocacy, was not presented as an obvious gain. Indeed, the definitions of success and failure were open to dispute. For example, if an intervention is stopped early, this can be seen as a failure of the intervention or a success of the design, which allows the early identification

of poorly performing arms. There might be discrepancy within a trial consortium as to whether or not this kind of 'failing' is a success or not.

Interdisciplinary communication

A recurrent theme in the interviews was the way in which ADs change the relationship between statisticians and clinicians. Whereas with fixed designs, statisticians are typically called on to provide a sample size estimation and analysis plan, with ADs, they were said to be more fundamentally involved in the design and implementation from start to finish. As a result, the dynamic and the communication between team members was changed, with a constant conversation needed about data and decision-making. This change was regarded positively, but was also thought to occasion some difficulties. In general, statisticians felt there was a lack of understanding about ADs and a sometimes naïve desire among investigators to use them regardless of their suitability. Equally, non-statisticians lamented the complexity of the statistics demanded by new designs and the communication challenges this posed. For example:

"I think one of the real challenges has been communication around this, because ... they're academic statisticians ...their focus is on developing methodology. And their ability to communicate to a group of clinicians whose research training is either basic science or is the extent that one gets in an MPH – that has been really, really difficult to bridge that gap." (KI023, Epidemiologist)

"We've come up with a very long list of how to define a treatment failure, you could spend a good two hours working through that and as clinicians you should be able to understand that. But it will take a while and clinicians probably prior to that didn't realise how complex it could be" (KI016, Statistician)

Various assumptions came to the fore, such as the idea that clinicians are unable to maintain equipoise, and that statisticians – for better or worse – play a

policing role in the trial. In order for ADs to function well, informants across the disciplines felt it was important that clinicians and statisticians act in collaboration rather than in consultation.

Regulatory and policy responses

Finally, there was concern among some informants that choosing an AD was risky, both in terms of the regulatory response, and in terms of the ability of policy makers to interpret the findings. This was particularly so in the case of Bayesian designs, as illustrated below:

"[N]obody else is taking the risk, we're the only ones who are taking the risk. I think the issue will really arise when it comes time to interpret these results for policy guidance by groups like the World Health Organisation, and I think we will probably have a new round of discussions about how to interpret and use those data" (KI023, Epidemiologist)

Indeed, Bayesian designs polarized debate among informants, with clear lines drawn between those who were uneasy about their use in late stage testing, and those who felt they provided a natural affinity with clinical decision-making.

DISCUSSION

This paper has presented insights from those working on, or advocating, adaptively designed TB clinical trials into the challenges and opportunities such designs provide. The findings add to the existing literature, which addresses technical statistical issues, by giving voice to the experiences of trial investigators, including statisticians, clinicians, and project managers. There are a number of limitations to this work. Firstly, most of the adaptive trials are in the planning stages and there is therefore limited lived experience with the challenges of implementation. It is possible that informants' views could change, particularly in the field of MDR-TB, once the proposed studies get underway. It will be important to conduct further research once these studies are realized.

A second limitation of this work is that we did not seek the views of those actively opposed to the use of ADs in TB drug development, nor can we say that our sample was representative of all those working on adaptive TB trials. Rather, this small, exploratory study provides early reflections on theory and practice in this emerging field from a group of key informants with first hand knowledge and experience. Its contribution is to provide sensitizing concepts for discussion moving forwards, including areas where further research is needed. Sensitizing concepts alert readers to issues in under-researched areas, and are useful not for their generalizability but for encouraging new ways of thinking about a topic ¹⁹. Following the thematic structure of the findings outlined above, we can categorise these broadly as the appropriateness of ADs for TB; the challenges implementing ADs in resource limited settings; and funding, research and policy cultures.

As our results highlight, the suitability of ADs for TB is a question which touches on the philosophical basis of evidence-based medicine and, linked to this, the interpretative processes of policy-making. ADs mark a break with the traditional view that the learning and confirming stages of experimentation be kept separate and that trials follow a fixed protocol designed to minimize bias. Instead, continuous learning is incorporated into the design as the trial progresses, allowing trialists to focus the experiment on the most promising trajectories. Rather than being a discrete entity, the trial becomes a relational process, with the scope to interact with other studies as they deliver new information. Against the history of phase III failures for shorter drug-sensitive regimens, regulatory openness to new evidentiary standards, and a policy environment hungry for new regimen roll-out, ADs are perceived as a timely and useful addition to the research toolkit in the TB community.

At the same time, those working on adaptive TB trials are encountering a range of logistical and ethical challenges, which have received short shrift in the trials literature to date. These issues – from regulatory capacity to review adaptive trials to how best to inform patients about participating in them – apply across disease areas and all parts of the world. In the case of TB, however, they are

exacerbated by the limited resource capacity in the settings in which such trials take place.

The challenges of frequent interim analyses and response adaptive randomization have been little discussed in relation to patients. In line with a recent study by Legocki et al ²³, informants in this research did not agree on whether informed consent in adaptive trials would be more complex. As Legocki et al observe this may reflect differences in approach to consent; where investigators believe it is necessary to share details about randomization or interim analyses, consent will likely be more complex than if a general statement is given. Lack of experience about ethical risks and patient perspectives on ADs, uncertainty about how much information to give patients, and disagreement over the complexity of the message suggest empirical research is urgently needed in this area. Qualitative research embedded in, or conducted alongside, adaptive trials should ideally be used to explore these issues, which may lend themselves best to an ethnographic approach.

Finally, ADs present challenges to the organization of trial research, from funding to team dynamics and the response of policy-makers – what has previously been called a “change-management challenge” ²⁴. Statistical changes to dealing with uncertainty need to be supported by funding mechanisms which allow for flexibility, interdisciplinary teams whose members communicate effectively with one another, and a policy-making forum receptive to new forms of evidence. The notion of developing drugs one at a time for tuberculosis is a thing of the past, but research cultures take time to change, along with the structures which underpin them. Inroads are being made by various bodies centrally involved in TB research; for example, the UK Medical Research Council has established eight Hubs for Trial Methodology Research, with an Adaptive Designs Working Group.

CONCLUSION

While statistical development of adaptive methods continues apace, research which focuses on the context of methodological change in RCTs is sorely needed. Twenty years ago, Rosenberger observed that “in medical experimentation we are dealing with human lives; therefore ethical and logistical considerations must always drive the mathematics” (p138). In TB research, the big picture of human suffering and the failures of drug development have indeed been the impetus for methodological innovation. What is now needed is an understanding of the fine-grained dynamics of how such innovations translate into practice.

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