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Investigator-initiated randomized controlled trials in infectious diseases: better value for money for registration trials of new antimicrobials

Mical Paul, Infectious Diseases Institute, Rambam Health Care Campus and The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

Stephan Harbarth, Division of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Angela Huttner, Division of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland

Guy E. Thwaites, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, UK and Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam

Ursula Theuretzbacher, Center for Anti-Infective Agents, Vienna, Austria

Marc J.M. Bonten, Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

Leonard Leibovici, Department of Medicine E, Rabin Medical Center, Beilison Hospital Petah-Tikva and Sackler Faculty of Medicine, Tel-Aviv University, Ramat-Aviv, Israel

Corresponding author

Mical Paul, MD

Head, Infectious Diseases Institute - Rambam Health Care Campus

Associate Professor, The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology

Email: paulm@technion.ac.il

Tel: 972-50-2062140

Summary: Costs of investigator-initiated trials are lower than those of industry-sponsored trials. We present our viewpoint on the sources of these costs and compare trials' aims and methods. We propose greater role for academic clinical trials networks, especially for antibiotic development.

Abstract

Randomized controlled trials (RCTs) conducted by the industry are expensive, especially trials conducted for registration of new drugs for multidrug-resistant (MDR) bacteria. Lower-cost investigator-initiated trials have recently been successful in recruiting patients with severe infections caused by MDR bacteria. In this personal viewpoint, we contrast the aims, methods and resulting costs of industry-led and investigator-initiated trials and ask whether contemporary registration trial costs are justified. Contract research organizations, delivering and monitoring industry-sponsored trials at a significant cost, have little incentive to make trials more efficient or less expensive. The value of universal monitoring of all trial data is questionable. We propose that clinical trial networks play a more influential role in RCT design and planning, lead adaptive risk-based trial monitoring, and work with the industry to maximize efficient recruitment and lower costs in registration trials for the approval of new antimicrobials.

Keywords: Phase 3 trials; New drug approval; Multi-drug resistant bacteria; Contract research organizations

A large difference exists between the costs of industry-sponsored trials and those of investigator-initiated trials. The differences in costs are by orders of magnitude and trial costs are ultimately borne by the public. We present our personal views on trials costs, focusing on drug development and approval for multidrug-resistant bacteria, the reasons underlying high trial costs, and suggest a framework for improving trial efficiency and lowering trial costs.

Trial costs

No specific information on the costs of industry-sponsored randomized controlled trials (RCTs) for antimicrobials is publicly available. [1] In estimates based on software used to support contract research organizations (CROs) and pharmaceutical sponsors in evaluating trial proposals, the reported median cost of phase 3 industry-sponsored RCTs conducted between 2010-2015 in all fields was $21.4 million, with a skewed spread (mean $34.4 million) and costs going up with increasing sample size, number of sites, regions and countries, number of subject visits, trial duration and emerging market activity [2]. A broad range of costs was also estimated for trials of new drugs approved by FDA between 2015-2016, with a mean cost of $48.9 (95% CI 25.0-62.7) million for active-drug controlled trials, as are all recent antibiotic-registration trials [3]. The costs went up with trial duration, sample size and assessment of clinical endpoints. More recently, the costs of phase 3 industry-sponsored RCTs of hospital-acquired and ventilator-associated pneumonia were reported [4]. The average cost for a typical HAP/ VAP trial was $89,600 per patient. The costs were significantly higher than the costs of oncology and endocrinology clinical trials, as expected given the limited time window from eligibility to recruitment in trials assessing antibiotics for acute bacterial infections. These again are not actual trial costs, but estimates based on enumeration and cost attribution to all trial elements, adjusted to multidisciplinary expert feedback. When examining the cost drivers affecting trial costs, an increase in the number of individuals screened

in order to randomize one patient yielded the highest impact on overall costs (estimated at $5700 per screened patient in HAP/VAP RCTs, considering trial size, number of sites, procedure costs and costs of recruitment) [4]. Indeed, trials addressing highly-resistant bacteria and severe infections encounter high screen failure rates; [5-7] the rate presented for the CARE trial assessing plazomicin vs. colistin-based therapy for bloodstream infections caused by carbapenem-resistant enterobacteriaceae, was more than 30 screened patients for 1 randomized, with a resultant trial cost of approximately $1 million per enrolled subject. [8]

External costs of investigator-initiated RCTs are more easily obtained, as the funding for the trial is frequently provided as publicly-funded academic grants. National grants for RCTs have a wide range. The Swiss National Science Foundation launched a call for investigator-initiated clinical trials addressing unmet medical and societal needs with a budget of about $10.3 million aiming to fund at least four trials. [9] The median budget for investigator-initiated RCTs funded by the Netherlands Organization for Health Research and Development (ZonMw) for more rational use of pharmaceuticals in clinical practice between 2007-2014 was about $0.5 million per trial. [10] In Israel, the Israeli Ministry of Science and Technology launched a call for clinical trials on novel agents to fight antibiotic resistance in 2018, with a budget of $170,000-340,000 per trial (actual funding of $113,000 provided per RCT). [11] European grants, targeting multinational collaborative projects, are larger. The FP7 call for investigator-initiated clinical trials of off-patent antibiotics funded two projects, MagicBullet comprising one RCT and AIDA comprising three RCTs, with a budget of $6.5 million per project. While these reflect the external resources, investigator-initiated trials rely also heavily on internal resources for wo/manpower and use the hospitals' and universities' infrastructures. Some investigator-initiated RCTs are performed based on internal resources without external funding; our investigator-initiated RCTs ranged from no external funding to $1.5 million for the FP7-funded AIDA trial (Table 1). [12-15] The highest external costs were

$3000 per recruited patient in the trials funded by the EU project [12, 16]. Similar and lower overall costs have been reported from other investigator-initiated RCTs [17]. Thus, even when considering the important contribution of internal resources to investigator-initiated trials, the contrast between investigator-initiated and industry-sponsored RCT costs is striking.

Differences between industry and investigator-initiated trials

There are large differences in the delivery of industry registration trials and investigator-initiated RCTs, explaining to some degree the differences in costs. [18] Industry trials pursue regulatory approval for a new medicine, while investigator-initiated trials typically compare already approved and commonly used drugs or other comparative effectiveness research. Eligibility criteria in industry trials are highly selective, resulting in recruitment of a small sample of all patients with the condition targeted. [19, 20] The safety monitoring is extensive, led by the regulatory requirements, and the datasets are exhaustive. Industry-sponsored trials typically recruit many centers, investing in the start-up and screening fees in all centers, with most centers recruiting very few patients and a few centers recruiting most patients (but typically not more than 10-20 patients per center). This does not allow building local expertise and clinical trials capacity in the trial's centers. The sites do not participate in the trial planning and their motivation for participation may be financial alone.

Investigator-initiated RCTs rely on investigators' partnership, interest, dedication and motivation to complete the trial. Generally, few study centers recruit many patients each. Eligibility criteria are broader, with investigator-initiated trials successfully completing trials that included patients with severe infections caused by carbapenem-resistant Gram-negative bacteria [12] or MRSA [14, 21] and patients with bacteremia caused by ESBL-producing enterobacteriaceae [22]. In our trials, data collection has

focused on the variables needed for data analysis, avoiding duplication, redundant information, and using validated scores for comorbidities and sepsis severity. The recruiting centers generally took part in the drafting of the protocol, understood the trial and identified with its aims. Typically, after a learning curve, the trial procedures became routine in the participating centers. The framework driving patient recruitment relied on academic responsibility and motivation rather than monetary incentive; this was possible when all study centers were involved in planning of the trial and had scientific motivation to complete the trial.

Monitoring in industry-sponsored RCTs is outsourced to CROs, while in investigator-initiated trials monitoring is frequently performed by academic clinical trials units linked to the researchers. Site monitoring and source data verification costs amounted to 18% of total phase 3 trials costs in one estimate [23]. The incentive of a CRO for the trial to proceed efficiently is questionable, driven by competition and business requirements. In our personal experience in Israel, CRO trial monitors have limited understanding of the trials' background, rationale and implications; thus they may not elicit enthusiasm or interest in the trial. The CRO personnel turnover rate is high. Universal checks of all trial data and source-data verification without regard to various data points' clinical relevance are unjustified. All data monitored are assigned the same level of importance. "Deviations" are assigned by the monitors and site investigators do not know how these deviations affect the analysis, and whether these will be used to exclude patients from intention-to-treat analyses. The cumulative time spent entering a patient's data into the trial's case report form by all players (local research assistant, the changing monitors and auditors) amounted to a total of 27 full-time equivalent days per patient, in the industry-sponsored trials in which we participated. In our investigator-initiated RCTs, those monitoring the study had a good understanding of the trials' background, importance and rationale. They had direct access to the principal investigator (PI). Data collection focused on the crucial variables for comparison

between the study groups and outcomes. Monitoring was performed in the beginning of the trial and sparsely later on, focusing on problematic sites and based on central inspection of the accumulating data by the primary investigators.

Improving trial monitoring

Monitoring has several objectives; some can be achieved internally by the local investigators and some would clearly benefit from external monitoring as these could be clouded by investigators' biases. The targets of monitoring and suggested pretrial activities are detailed in Table 2.

Traditional trial monitoring relies on comprehensive onsite monitoring and source data verification of 100% of collected data. Alternative strategies have been proposed to improve efficiency and lower costs of monitoring. Central monitoring is performed by reviewing aggregate data throughout the trial using analytics to detect mistakes, discrepancies and poorly performing sites. Central monitoring may more reliably and efficiently detect transcription errors using computerized techniques, and allows detecting patterns within and across trial sites. [25] Risk-based monitoring predefines critical data and processes for monitoring. It is trial-specific, requires expertise for prospective analysis of the trial data and definition of the critical data. It requires early collaboration between the academic and monitoring leads of the trial. [26] As an example, the monitoring plan may predefine a certain percentage of participants from all sites whose charts will be examined at random, in a centralized "first pass," for source-data verification involving variables that are essential to the trial's validity and outcome. Depending on the number of transcription errors, deviations, or other findings, either the same percentage or a higher percentage of charts is reviewed at the next monitoring visit. The results allow monitors early identification of trial sites, investigators and/or data-collection points that may require more intensive scrutiny. The process should be iterative, with additional random checks to capture trouble spots not previously identified in

earlier passes. Thus, monitoring can be risk-based and adaptive, focusing on high-value data points and responsive throughout the trial to sites' performance. An adaptive risk-based monitoring strategy has been found to be more efficacious and markedly cost-saving compared to the standard CRO monitoring. [27] Though guidance on risk-based trial monitoring has been provided by the FDA since 2013, it has not become standard practice in industry-sponsored RCTs. [28] FDA recently issued guidance on optimization of safety-data collection using a selective approach for some late-stage pre-approval trials. [24] The guidance allows consideration in collection of data on non-serious adverse events, routine laboratory tests, concomitant medications, physical examinations and all vital signs and electrocardiograms, currently collected comprehensively and non-selectively in all phase 3 antibiotic trials.

Quality of trials and risk of bias

Higher quality of industry-sponsored trials vs. investigator-initiated studies is presumed, mainly on the basis of these differences in data collection and monitoring. [18] Yet, a Cochrane review examining the effects of industry sponsorship on favorable outcomes and risk of bias found no association between sponsorship and randomization methods, follow-up or selective outcome reporting. [30] Industry-sponsored trials were more frequently double-blinded. Modified intention-to-treat analyses, with post-randomization exclusions, were more common in industry-led RCTs than in trials funded by not-for-profit organizations (adjusted OR 7.41, 95% CI 3.14 to 17.48). [31] Intensive monitoring ensures minimal missing data in industry-sponsored RCTs; in our pragmatic studies, certain data were missing, documentation was lacking and follow-up was not perfect. However, the critical data necessary for comparisons and primary outcome evaluation were universally available (except for patients lost to follow-up). In industry trials, the trial database is held by the company; in our trials the database was shared by all participating centers who could review the data and data analysis. While external validity may not be an objective in industry-sponsored trials, investigator-initiated RCTs typically target and

include the clinically-relevant patient population. [19, 32] Investigator-initiated trials usually take longer to complete and are on average smaller than industry-sponsored trials. If publication status is a criterion for quality, more industry-sponsored studies appear to go unpublished than investigator-initiated studies, at least among those registered. [33-36] Patients' safety, autonomy and privacy are paramount in all RCTs. While investigators leading studies may have *a priori* beliefs that may bias trial results,if the trial is not designed and conducted rigorously, overall, industry sponsorship was more strongly associated with favorable efficacy results and conclusions than sponsorship by other sources. [30]. Altogether, these differences in trial methods do not explain the large cost difference between industry-sponsored and investigator-initiated trials.

Improved efficiency at lower costs

Comparing industry-sponsored registration trial costs to investigator-initiated RCT costs highlights the potential for cost saving in industry-sponsored trials. Many of the requirements from industry trials are dictated by the guidelines for new drug approvals issued by regulatory agencies (FDA and EMA). The recent FDA guidance on selective safety monitoring in late-stage trials [24] and broadening eligibility criteria [37] can improve efficiency and relevance of antibiotic-registration trials. Academic-public-private partnerships have shown the potential of such a model to improve research capabilities (e.g. TB Alliance, Medicines for Malaria Venture, COMBACTE, ECRAID). More should be advanced in the field of antibiotic development and the collaboration between the academic partners and the industry should be optimized to allow the academic partners to take an actual role in the study design and analysis. [38] Independent academic investigators should take part in phrasing the research question, planning the trial and writing the protocol to try and address as far as possible within the regulatory requirements the relevant population and the outcomes that matter to patients. Their involvement should allow a risk-

based monitoring strategy. We propose that academic international high-quality clinical trial networks be allowed to deliver important aspects of trial conduct now executed by CROs. Academic centers of excellence should be identified for their ability and experience to lead RCTs to the required regulatory standards. Competitiveness might lead CROs to reduce costs and improve efficiency. Appropriate resources will allow academic networks to adhere to the standards required for registration trials. The criteria for selection of the organization that will run the trial should consider the efficiency, interest and enthusiasm of participating centers to collaborate with the organization (proposed criteria in Table 3).

In summary, industry trial costs have increased unreasonably, especially for trials focusing on infections caused by multidrug-resistant bacteria. We call for transparent reporting of trial costs in the study registries or with the final publication. We believe that it is the obligation of the academic clinical trials community to support high-efficiency, lower-cost RCTs to support antibiotic development and approval.

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Table 1: Authors' selected investigator-initiated trials (completed 2014-2018)

Trial	N patients/ hospitals	Trial duration (months)	External funding ($)
Intravenous vs. subcutaneous G-CSF for neutropenia [15]	120/1	22	None
Trimethoprim-sulfamethoxazole vs. vancomycin for invasive MRSA infections [14]	252/ 4	82	32,670
Seven vs. 14 days of antibiotic treatment for Gram-negative bacteremia [13]	604/ 3	56	None
Colistin vs. colistin + meropenem for invasive carbapenem-resistant Gram-negative infections [12]	406/ 5	39	1.5 million [1]
Fosfomycin compared to nitrofurantoin for cystitis [16]	513/ 3	42	1.3 million [1]
PIRATE project: randomised controlled trial for decreasing overuse of antibiotic therapy in Gram-negative bacteraemia [39]	500/3	27	412,000
Gatifloxacin versus ceftriaxone for uncomplicated enteric fever in Nepal: an open-label, two-centre, randomised controlled trial. [40]	239	32	254,000
Adjunctive rifampicin to reduce early mortality from *Staphylococcus aureus* bacteraemia (ARREST trial) [41]	758	46	1.64 million

A randomised double blind placebo controlled phase 2 trial of adjunctive aspirin for tuberculous meningitis in HIV-uninfected adults [42]	120	20	292,000

[1] The costs for these trials comprised of comprehensive PK and microbiological assessment of resistance, resistance mechanisms, fitness, synergy studies and more.

Table 2: Targets of trial monitoring

Objective	**Timing and place of monitoring**	**Preference for internal/ external monitoring [1]**
Ensure that inclusion/ exclusion criteria are met and ethics of patient recruitment are respected	Critical at start of the trial in real time and continue monitoring in real time onsite	External
Ensure follow-up procedures and outcome definitions are well understood	Critical at start of the trial in real time and continue monitoring in real time onsite	Internal
Ensure uniform definitions for study variables across sites	Important at the start of the trial. Can be done remotely	Internal
Ensure concordance between recorded and actual outcomes	Not necessarily in real time for objective outcomes (e.g. mortality); real time for subjective outcomes	External
Check data entry for mistakes/ inconsistencies	Not necessarily in real time, though first visit should occur early to ensure best practices. Can be performed remotely using centralized algorithms	Internal/ centralized external
Monitor ethics approvals	Periodic, remotely	Centralized external

[1] Internal monitoring by local PI; external monitoring by personnel independent of the funder and unrelated to the monitored site and local investigators at the study site; centralized external monitoring can be done by independent personnel but remotely.

Table 3: Proposed criteria for selection of an organization to run a clinical trial network and collaboration methods with sponsors

Criteria for selection
No conflict of interest vs. the sponsor or drugs investigated
Experience in performing clinical research
Expertise in the field of the trial
Qualified personnel to run the trial and perform monitoring
Ability to teach monitors the trial's background, rationale, design and importance
Favorable cost/ budget ratio
Networks' pre-trial activities
Input in the development of the study protocol
Developing a risk-based monitoring strategy fit for the trial
Devise criteria for site selection
Site selection based on criteria and acquaintance with researchers