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Original Research Article

Challenges and threats of investigator-initiated multicenter randomized controlled trials: the BACE trial experience

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ABSTRACT

Background: Investigator-initiated clinical research has become a complex environment. Increasing administrative tasks and costs, imposed by stringent regulatory demands, risk to reduce this creative, independent and indispensable research field. The objective of the present study was to illustrate the burden of non-scientific challenges associated with an investigator-initiated multicentre randomized controlled trial, based on the Belgian trial with azithromycin for Chronic obstructive pulmonary disease (COPD) Exacerbations requiring hospitalization (BACE) trial experience.
Methods: The trial enrolled 301 patients with COPD, hospitalized for an acute exacerbation between 2014-2017, and assessed the potential of azithromycin, an off-patent antibiotic. Key experienced challenges were complemented with registry data from the Clinical Trial Centre of the University Hospital Leuven to outline the local clinical respiratory research field, quotations for the trial protocol obtained from 3 pharmaceutical companies to provide insight into the budget restraints and a participation survey to capture the consortium's perspective.
Results: 60% of the required sample size was enrolled. Key challenges included trial implementation, study drug and database management. Industry-initiated trials dominated the local research field (61%), whereas investigator-initiated prospective interventional and multicenter trials accounted for 19% and 13%, respectively. The triple quotation revealed the BACE trial to require 1.6 to 2.1-fold the amount when executed by the pharmaceutical industry. The survey identified the lack of a local study team as an important obstacle for participation, along with inadequate financial compensation and excessive administrative workload.
Conclusions: Without an adaptation of current regulatory and funding policies to overcome non-scientific challenges, investigator-initiated clinical research is risking to further decline.

Keywords: Academic, Clinical research, RCT, Challenges, Burden, Pharmaceutical industry

INTRODUCTION

Randomized controlled trials (RCT) form the cornerstone of evidence-based decision making and are considered the gold standard for clinical research.[1] Compared to industry-initiated trials (with a commercial sponsor), non-commercial trials initiated as part of academic research (investigator-initiated trials, IIT) are more likely to test established rather than new drugs and devices, evaluate protocols and guidelines and examine patient and family-

centered outcomes.[2] Lack of monetary incentive for the industry and market pressure to develop patentable drugs often leave important issues unresolved, and available and affordable potential unexplored.[3] Such IITs, honoring the broad concerns of the public, physicians and healthcare systems are unsolicited and characterized by a subset of highly persistent clinicians with the motivation to advance medical and scientific knowledge. Testing existing treatments through large RCTs in routine clinical practice can optimize generalizability, expand product knowledge and provide the best evidence for effectiveness.[4] Evidence provided by independent trials, whose endpoints reflect clinical need and significance, carry greater weight than industry sources of data and have the potential to change clinical practice.[1]

In recent years, however, regulatory (often bureaucratic) hurdles have increased significantly, with authorities and auditors no longer differentiating between the industrial and academic setting.[5] Investigators are required to conduct the trials under the same rigorous standards, while the entire sponsor responsibility befalls the initiating investigator and a variety of staff of his institution, in addition to a full-time job. Although centers of clinical excellence, only a few organizational structures of universities and (associated) hospitals are capable to take on all responsibilities, tasks and duties required by Good Clinical Practice for the complete organization of IITs. Clinical Research Organizations, developed to accommodate these complex tasks, have professionalized the field, however, not without increasing its costs. With a widening gap between the cost of research and available funding opportunities- often with limited chances of success- the time-consuming process of writing a research proposal, as well as dire publication prospects in case of negative results are leaving clinicians discouraged from or unwilling to engage in those phase 3 trials that ultimately matter to patients. Whether commercial or non-commercial, all clinical trials must comply with adequate ethical and methodological standards. However, guidelines should allow consideration for trial and context-specific challenges with the purpose of increasing the chances of success and enhancing the number of conducted IITs. This can only be achieved if all parties involved increase transparency into the clinical research process and its inherent challenges.[6]

Based on our experience in the trial Belgian trial with Azithromycin for Chronic obstructive pulmonary disease (COPD) Exacerbations requiring hospitalization (BACE) -a national investigator-initiated multicenter RCT, assessing the potential of azithromycin, an off-patent antibiotic- we provide insight into our research efforts to supplement a large clinical trial. Key experienced non-scientific challenges were identified and complemented with registry data from the Clinical Trial Centre of the University Hospital Leuven to outline the local clinical respiratory research field, quotations for the trial protocol obtained from 3 pharmaceutical companies to provide insight into the budget restraints compared to industry-initiated trials and a trial participation survey to capture the consortium's perspective. These insights may contribute to the sensitization of regulatory and funding agencies to the demands of investigator-initiated clinical research and aid future clinical investigators in the field.

METHODS

BACE trial

The BACE trial protocol was initiated by a physician researcher of the service of respiratory medicine of the University Hospital Leuven (Leuven, Belgium) and designed in collaboration with the University Hospital Ghent (Ghent, Belgium). The objective was to set-up a national multicenter randomized double-blind placebo-controlled trial, aimed at assessing the overall benefit/risk ratio of a 3-month intervention with low-dose azithromycin -an antibiotic that has been off-patent since 2006- for the acute treatment and prevention of COPD exacerbations. The protocol was designed to be embedded in routine clinical practice following a severe exacerbation requiring hospitalization, and the treatment failure rate within 3 months was evaluated as primary endpoint. The trial required the enrolment of 500 patients to show a relative improvement of 35%. Additional details on the study protocol (NCT02135354) and obtained results are described elsewhere.[7,8]

In December 2012, the BACE trial consortium was established consisting of respiratory physicians from 5 academic and 14 non-academic hospitals, with the University Hospital Leuven as lead centre. The protocol was submitted in February 2013 to the program for applied biomedical research (TBM, founded by the Flemish government agency for innovation by science and technology, IWT) and received the maximum funding budget (€1.000.000) and duration (48 months) in June 2013. The preparatory phase was scheduled to begin in October 2013, patients to be recruited between April 2014 and April 2016, and the clinical follow-up to be completed by December 2016. Publication of the trial results was scheduled for October 2017 after database cleaning, statistical analyses and the manuscript writing-submission-revision process, anticipated to take respectively 3, 2 and 4 months.

The Catholic University of Leuven (KUL), represented by the KUL Research and Development, and the associated University Hospital Leuven took responsibility for the legal sponsorship, including contractual aspects and financial management of the research project. The execution of all trial related activities (such as initiation visits, site support, data-monitoring and database cleaning) was coordinated- in addition to local enrolment- by the 'central' operational staff, consisting of 2 full time equivalents (FTE): 1 PhD student at the lead centre under the supervision of the initiating investigator and 4 clinical trial coordinators at the University Hospital

Ghent, each allocated for 25% to the trial. The lead centre took responsibility for all correspondence with the competent authorities (CA) and ethics committees (EC), the bi-monthly communication within the consortium, the 6-monthly scientific reporting to the IWT, management of the investigational medicinal product (IMP) and electronic case report form (eCRF), and coordination of the self-billing procedure by the consortium, in addition to national and international dissemination of scientific results.

Key experienced non-scientific challenges were identified based on the unforeseen increase in workload and delays in achieving the expected milestones.

Research climate

To outline the local research climate in the field of respiratory medicine, registry data were provided by the Clinical Trial Centre of the University Hospital Leuven, the largest university hospital in Belgium. Data were obtained on the number of industry and investigator-initiated trials registered between 2011 (start of registration) and 2016, specified for trial design and set-up.

Budget restraints

To provide insight into the budget restraints compared to industry-initiated trials, 3 major pharmaceutical companies investing in the field of respiratory medicine were asked for a quotation of the BACE trial protocol. The quotations were compared on the costs to cover the sample size, trial organization and monitoring.

Consortium's perspective

To capture the consortium's perspective, a BACE trial participation survey was designed to explore the factors limiting and facilitating the contributions of the participating sites. The survey was composed of questions exploring their previous experience in industry and investigator-initiated RCTs, followed by questions evaluating their views prior to and after BACE trial participation, on a three-point scale (agree, neutral and disagree). The questions respectively addressed perceived obstacles for IIT participation, reasons for BACE trial participation, feasibility considerations upon signing the intention agreement; and the enrolment experience, areas of experienced difficulties and pleasure and overall satisfaction. The survey was provided by mail to the consortium at the end of the enrolment period, with exception of the initiating and collaborating investigator, and was requested to be completed jointly by all local members involved to capture the BACE trial experience in its entirety. Two hospitals which were not successfully initiated did not contribute to the views after participation.

RESULTS

BACE trial

The actual preparatory phase began in December 2013. By February 2014, 2 hospitals had withdrawn from the consortium as participation was no longer considered feasible and the protocol was submitted simultaneously to the CA, the central and 16 local ECs. Due to delayed reporting by 3 local committees, ethical approval for the entire consortium required an amendment for site addition, and was obtained in May 2014. Approval of the final protocol version was obtained in June 2014, following the submission of 2 additional amendments, incorporating suggestions from participating hospitals to increase local feasibility and a recent update in the international treatment guidelines. In parallel, the development of the eCRF, contractual aspects and the procurement, randomization and distribution of the IMP were finalized, respectively by July and August 2014, in addition to the assembly of the investigator and pharmacy site files containing the bilingual study material and legally required documents. In August 2014, after notification and approval of the central EC, recruitment started in the lead centre only, to test the implementation of the study material, protocol and eCRF, whereas the consortium was initiated between September and October 2014. One hospital declined initiation due to the deprivation of local human resources, preventing further involvement. Despite bimonthly newsletters encouraging active participation, personal inquiry of local difficulties preventing recruitment and hosting an investigator meeting to provide solutions, enrolment in May 2015 was lower than anticipated and it was opted to foresee in the statistical analysis plan an interim analysis for efficacy and futility after 300 inclusions, based on a new power calculation extrapolated from the observed lower drop-out rates and higher proportion of primary endpoints reached. Unresolving slow recruitment resulted in the submission of an amendment to the CA and involved ECs for the addition of 3 new hospitals, expanding the consortium to a total of 20 in August 2015. Activation of one hospital, however, remained unsuccessful as participation was no longer considered feasible by the local medical director. Furthermore, as one of these hospitals was located in a different language area in Belgium, a trilingual country, this required an amendment for the approval of all translated study material, in addition to the restart of contractual, IMP and eCRF activities. In May 2016, the recruitment prospects and possible complications of the IMP expiring in November 2016 were evaluated. Based on the remaining funds, the enrolment contributions and resource availability in the participating hospitals, it was opted to limit recruitment and IMP re-supplementation to 7 hospitals. In April 2017, a total of 301 patients were randomized (60% of the initial pre-set sample size) by 15 actively participating hospitals in the consortium (≥1 inclusion), 131 (44%) of which were included by the lead centre. The enrolment progress is shown in Figure 1. Due

to the cumbersome recruitment and the unavailability of additional funds to prolong the trial, it was decided to stop enrolment early and perform the final analysis when all 301 patients reached their end-of-trial follow-up, which was completed in January 2018. Data-monitoring was started in August 2016, the database locked in March 2018 and the statistical analysis plan implemented in May 2018. From October 2017 onwards (the end of the funding period), all research efforts were continued by the lead centre using own resources. The projected and realized timelines for the main milestones and work packages are presented in Figure 2.

Table 1: Clinical trial registry data.

A.								
	Initiator	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total**
	Industry	17	13	22	28	26	25	131
	Investigator	14	17	9	13	26	6	85
	Total	31	30	31	41	52	31	216
B.								
Industry-initiated	**Trial design**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total**
	Prospective interventional	17	12	20	27	25	21	122
	Prospective non-interventional	0	0	1	1	1	3	6
	Retrospective	0	1	1	0	0	1	3
	Total	17	13	22	28	26	25	131
Investigator-initiated	Prospective interventional	4	10	5	7	14	1	41
	Prospective non-interventional	7	2	4	3	9	3	28
	Retrospective	3	5	0	3	3	2	16
	Total	14	17	9	13	26	6	85
	Final total	31	30	31	41	52	31	216
C.								
Industry-initiated	**Trial set-up**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total**
	Monocenter	1	0	1	0	5	1	8
	Multicenter	16	13	21	28	21	24	123
	Total	17	13	22	28	26	25	131
Investigator-initiated	Monocenter	9	12	6	7	19	4	57
	Multicenter	5	5	3	6	7	2	28
	Total	14	17	9	13	26	6	85
	Final total	31	30	31	41	52	31	216
D.								
Prospective interventional, drug-related trial								
Industry-initiated	**Trial set-up**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total**
	Monocenter	0	0	0	0	3	0	3
	Multicenter	16	11	19	26	21	20	113
	Total	16	11	19	26	24	20	116
Investigator-initiated	Monocenter	1	2	0	0	0	0	3
	Multicenter	0	0	1	2	2	0	5
	Total	1	2	1	2	2	0	8
	Final total	17	13	20	28	26	20	124

Values are presented as number Trial registry data between 2011 (start of registration) and 2016 were obtained from the Clinical Trial Centre of the University Hospital Leuven. Data are presented according to (A) the trial initiator, which is further specified for (B) trial design and (C) trial set-up. Data on prospective interventional drug-related trials are presented (D) to provide insight into the number of yearly registered trials designed according to the BACE trial concept.

Key experienced difficulties

Trial implementation

Within the consortium, the core activities (local EC submission, enrolment, source and eCRF completion) were largely supplemental responsibilities carried out by the local investigator with full-time clinical obligations or were assigned to a variety of staff in addition to a full-time job. For every inclusion, the local investigator received a financial compensation of €500 to cover the trial related costs which were not to be charged to the patient and the costs of the supporting services involved. Several inquiries regarding additional financial compensation were received during the trial conduct, as the remaining 25% insufficiently compensated the requested efforts for patient enrolment, source and eCRF management. The complexity of the trial protocol further

contributed to the workload, in addition to the eCRF updates and the investment of local human resources during the data-monitoring phase. As the funding to cover the site payments was originally budgeted for a total of 500 inclusions, and the final analysis would be performed in 301 patients, a budget rearrangement allowed the participating hospitals to be compensated with an additional €200 for every past and future inclusion. To assist with the data-entry of the local 131 inclusions, the lead centre was reinforced between February 2016 and September 2017 with a 0.5 FTE. The University Hospital Ghent was reinforced between August 2016 and December 2017 with a 0.43 FTE to assist with data-monitoring and database cleaning.

IMP management

Managing the IMP entailed its procurement, randomization and distribution within the consortium. As no hospital pharmacy in Belgium (including university hospital pharmacies) had authorization for the production of placebo; the production of active treatment, placebo comparator and its packaging were outsourced to a specialized company. In May 2014, an amendment submitted to the CA and notification to the central EC were approved, requesting the randomization and distribution in Belgium to be carried out by the hospital pharmacy of the University Hospital Ghent, which acquired the necessary accreditation in April 2014. A total of 600 boxes of IMP for individual use were manufactured in 2 batches. With exception of the lead centre, all hospitals were supplied in September 2014. Re-supplementation was organized taking the local enrolment progress, the expansion of the consortium and the IMP expiry dates into account; and was coordinated 3 times in 2015 and twice in 2016. With dire enrolment prospects and the final batch of IMP expiring in November 2016, a restart of the manufacturing process was required to prevent enrolment stopping prematurely due to a lack of IMP. Unfortunately, contract negotiations with the initial manufacturer remained pending, and were ultimately cancelled in July 2016 as a recent inspection prevented the prolongation of the required accreditation. Following contract set-up and negotiations, an amendment was submitted in October 2016 to the CA and notification to the central EC for the approval of a new IMP manufacturer, accredited in April 2015. A total of 80 boxes of IMP for individual use were manufactured, and distributed over 7 selected hospitals in December 2016, allowing enrolment to recommence after an interruption of 1.5 months. Of the 680 boxes of IMP, a total of 379 had remained unused in April 2017, at a manufacturing cost of €55 per box (not including taxes, nor the randomization and distribution costs).

Table 2: Cost quotation for the BACE trial protocol.

Quotation by	KU-UZ Leuven	Pharmaceutical company 1	Pharmaceutical company 2	Pharmaceutical company 3
Fee per inclusion	500	1.730	1.725	2.095
Total (n:500)	250.000	865.000	862.500	1.047.500
Trial organization	409.900	286.075	254.275	149.000
Trial management	√	-	√	-
Protocol writing	-	√	√	-
CA and EC submission	√	√	√	-
eCRF development	√	√	√	√
IMP procurement	√	-	-	-
IMP randomization	√	-	√	-
IMP distribution	√	-	√	-
Local start-up fee	-	√	-	-
Close-out	√	√	-	-
Statistical analysis	√	√	√	-
Reporting	√	√	√	-
Data-monitoring	340.000	993.027	630.000	360.000
Final total (€)	999.900	2.081.602	1.746.775	1.556.500

Obtained from the BACE trial sponsor (KU-UZ Leuven) and 3 major pharmaceutical companies, active in the field of respiratory clinical research. √: included costs; -: not included costs. CA: competent authorities; EC: ethics committee; eCRF: electronic case report form and IMP: investigational medicinal product.

eCRF management

The trial protocol was distilled into English worksheets, which were supplied to the consortium and served as template for the eCRF development. A custom-made eCRF was commissioned and tested by the lead centre following the local enrolment start. Though well-suited to the operational needs and trial procedures, the sole involvement of the lead centre resulted in significant delays due to the increased workload to resolve discrepancies which were only revealed upon the start of the data-monitoring phase and the implementation of the statistical analysis plan. In addition to its development and maintenance, the web-application required

unforeseen updates for the refinement and clarification of data, an expansion due to the site additions to the consortium, several adjustments to accommodate the statistical analysis plan and the development of a specialized platform to facilitate remote data-monitoring and database cleaning. The lack of a program to perform automated consistency checks (standard embedded in commercially available software tools, and indispensable for data-validation) further delayed the implementation of the statistical analysis plan.

Research climate

Between 2011 and 2016, the local respiratory clinical research climate consisted of 61% industry-initiated trials, whereas investigator-initiated prospective interventional and multicenter trials accounted for 19% (vs 56%) and 13% (vs 57%) respectively (Table 1). Notably, only 5 prospective interventional drug-related multicenter trials, including the BACE trial, were initiated by an investigator between 2011 and 2016 compared to 113 by the industry.

Budget restraints

While having received approximately €1 million from the IWT, the triple quotation revealed the BACE trial protocol to require 1.6 to 2.1-fold the amount when executed by the pharmaceutical industry (Table 2). Notably, this is an underestimation given the incomplete quotations regarding the trial organization cost. In the BACE trial, this cost was quoted to require 41% of the funding budget, not accounting for the protocol writing and trial start-up, commonly compensated by the industry. Underfunded in the BACE trial were the budgets foreseen to cover the sample size and data-monitoring costs, the workload of which would have had to been compensated respectively on average with a 3.7 and 2-fold the amount in the industry.

Consortium's perspective

A summary of the consortium's perspective is given. Full insight is provided in the online supplementary appendix.

Prior to the BACE trial participation

Within the consortium, 83% of the investigators (n:18) had prior experience of participation in industry-initiated RCTs, whereas in investigator-initiated RCTs, 50% had experience as a participating and 17% as an initiating investigator. The lack of local support (72%), limited financial compensation (67%) and excessive administrative workload (61%) were considered as main obstacles for IIT participation. Main reasons for BACE trial participation were the importance of the study aims from a clinical perspective (100%), to support the need for more academic research (83%) and a sign of collegiality to the steering members (72%). Notably, only 33% considered the availability of local support and the decision of the local team as a main reason for participation.

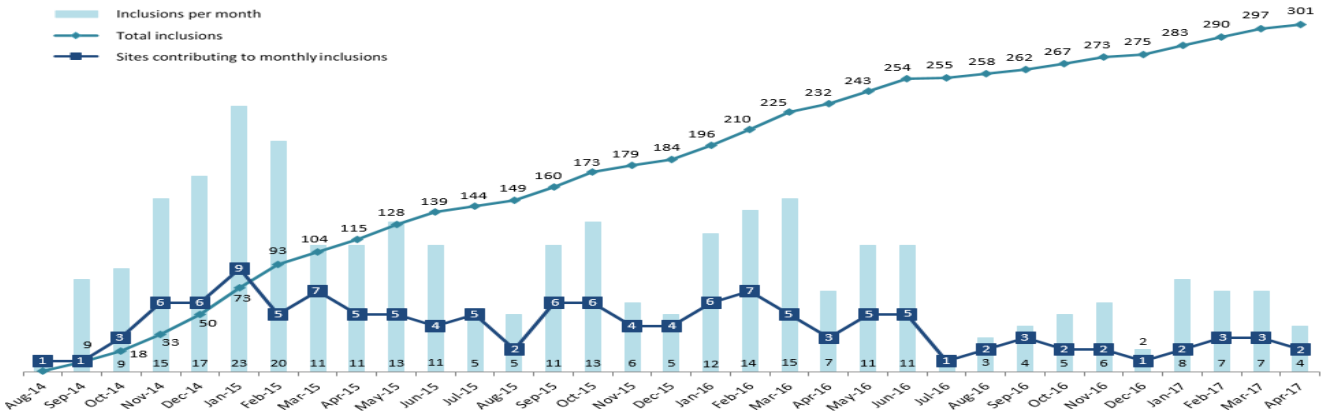

Figure 1: BACE trial enrolment progress.

Values are presented as number. The enrolment period commenced in the lead centre and Consortium respectively in August and October 2014, and was terminated in April 2017.

After BACE trial participation

As non-scientific challenges, 50% of the consortium (n:16) considered the administrative workload as excessive, and local support as insufficient, and 38% experienced excessive clinical workload. Remarkably, 50% experienced unexpected circumstances hindering participation and 44% reported a loss of enthusiasm as enrolment needed to be prolonged. 75% of the Consortium experienced pleasure from participating in a study that matters, 63% from the reduced administrative burden and 56% from the potential participation in publications. While only 25% considered their own contribution a success, 67% would participate in an investigator-initiated RCT again and 11% would firmly decline. Participation of the remaining 22% is dependent on the administrative workload and appropriate financial compensation to cover the cost for the necessary local support, in addition to the goodwill of colleagues to fulfil the role of sub-investigator.

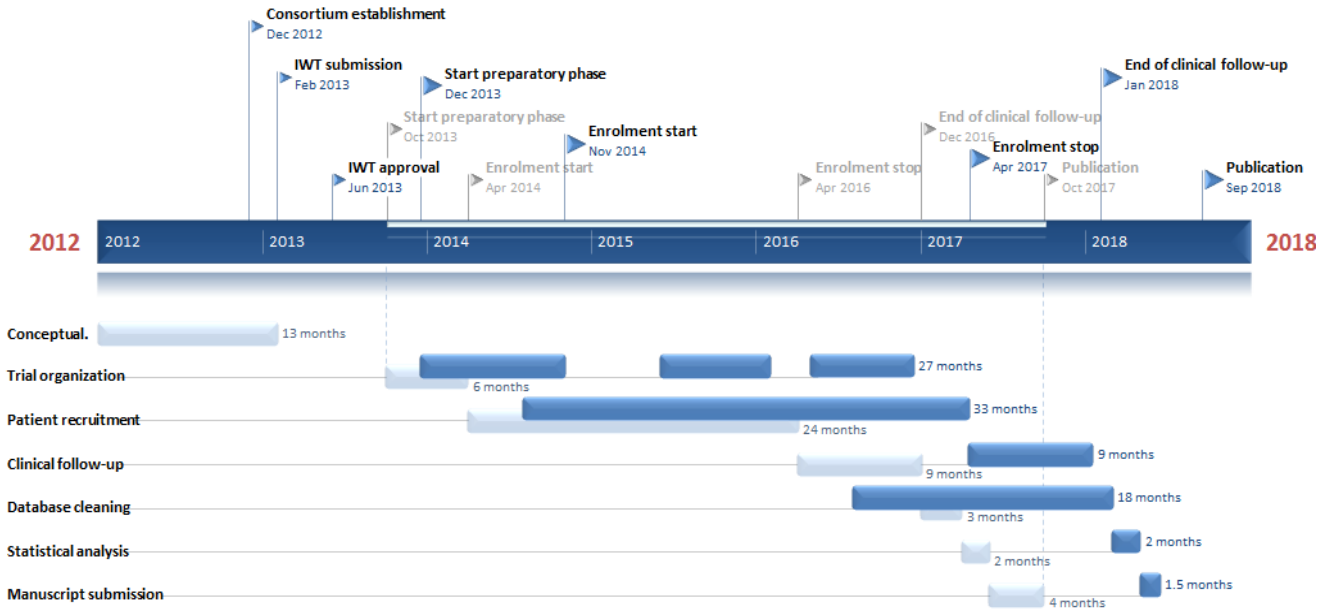

Figure 2: BACE trial protocol timelines.

The projected (light blue) and realized (dark blue) timelines are presented for the main milestones (flag) and work packages (bar). The 48-month funding duration (from Oct-2013 up to Oct-2017) is depicted with a full white line.

DISCUSSION

To sensitize the European Commission, national regulatory and funding agencies, and future clinical researchers to the inherent challenges of investigator-initiated clinical research, insight was provided into the conduct of the BACE trial, a national investigator-initiated multicenter RCT.

The implementation of the trial protocol, IMP and eCRF management was identified as the key non-scientific challenges which primarily delayed the expected milestones. Between the notification of funding approval and the time it was received, the initiating investigator lacked the necessary time to engage sufficient staff for the implementation of the trial protocol. In industry-initiated trials, the range of required activities is spread across different specialized units, such as planning, legal, financial, regulatory and ethical affairs, monitoring, database development and validation, data review and cleaning, and pharmacovigilance.[9,10] These departments are at the sponsor's disposal, maintain all up-to-date information and are attuned to one another and key activities can be outsourced as needed to Clinical Research Organizations. In the BACE trial, these activities were concentrated in a small unit and coordinated by a single person as part of a PhD trajectory. Adhering to these many requirements is a significant challenge for (multicenter) IITs. Every delay incurred increases the time cost of the trial and decreases its overall efficiency, but more importantly, jeopardizes the feasibility of trial participation within a consortium.[11] The long duration between signing the Intention Agreement (December 2012) and the initial submission of the protocol to the CA and ECs (February 2014), and site initiation (October 2014), resulted in the withdrawal of 3 hospitals (16%), a deficit which- a deficit which - despite best efforts- could not be restored. The long pre-study period was due to the complexity of preparatory activities, ranging from the finalization of the organizational and contractual aspects to the full set-up of the consortium. While indispensable to ensure local feasibility, it also necessitated the submission of a protocol amendment for it to be up-to-date with the changing international treatment guidelines for COPD. Beyond the trial implementation, IMP management and the lack of a standardized eCRF serve as good examples of the additional challenges met by IITs. While the sponsor in industry-initiated trials is often the manufacturer of the IMP, initiating investigators are dependent on contract manufacturers, increasing the administrative workload and often causing unexpected delays. From its procurement and timely distribution, to supervising the expiry dates, managing the IMP is one of those many vital tasks with little reward for an investigator. However, if these activities are done by (clinical) researchers, energy and funds are being diverted to administration, impacting on the success of the research efforts. A significant proportion is also directly linked to the complexity of the eCRF. To handle the large amount of data in a (multicenter) clinical trial, a standardized eCRF tailored to the statistical analysis plan is indispensable. For it to reduce the workload of identifying, reviewing and resolving discrepancies and increase the efficiency of statistical analyses and output generation, a close collaboration with the involved biostatistician is required during its development. To export an error-free, valid and statistically sound database, the clinical data management process should be started early-on and ideally the eCRF should be tested

with dummy data before its application to the real data capture. In addition to the burden of the initiating investigator, the participation survey revealed a discrepancy between the expectations of consortium members prior to participation and their performance during trial conduct. This required additional efforts that needed to be undertaken to engage new centers in an attempt to increase patient enrolment.

The BACE trial experience also highlights that not enough resources are made available to IITs to overcome the non-scientific burden, thereby challenging its successful undertaking. This message is hardly new and has resulted in fewer clinicians entering the research field. If it were not for the TBM program (founded in 2006 by the IWT), there would have been no funding opportunity in Belgium for this advanced application-driven biomedical research with distinct social applicability, in which the industry is not or very little interested. In 2011, the maximum project duration was extended from 3 to 4 years, and the maximum budget raised from €750.000 to €1.000.000, thus increasing the annual budget from €5.000.000 to €6.800.000 in 2013.[12] While efforts are being made to accommodate clinical research with longer durations and allow applicants to collect sufficient critical mass, they cannot keep up with the ever increasing costs of clinical research. Moreover, the episodic nature of grant proposals will never allow IITs to compete with the industry, which we see reflected in the registry data and the triple quotation with rough estimates revealing that at least a 2-fold the received budget would have been required if the protocol were to have been executed by the industry. In the TBM impact analysis of 2013, 20% of the survey respondents (particularly researchers engaged in clinical trials) still considered the duration too short, making multi-institutional studies practically impossible.[12] 'Stop clock' procedures could to some extent overcome this problem without inflating the research budget, however, will not provide a solution for costs such as salary.

Initiating investigators are often insufficiently supported by their academic institutions and are left largely to their own devices to implement and execute the trial protocol, and ultimately achieve their utilization goals.[11] In the BACE trial, the research goal was successfully secured as a result of the efforts which extended above and beyond the protocol. While the lack of local support was considered the main general obstacle for IIT participation (72%), only 33% of the consortium allowed its availability to determine their motivation to participate in the BACE trial. Despite this strong 'mind over matter' attitude, the consortium as well as the initiating and collaborating hospital required reinforcement to overcome non-scientific burden, in order not to undermine the data quality.

Academia should uphold high scientific and methodological standards, as independent clinical research has considerable impact on clinical practice.[10] It is our believe, however, that investigator-initiated multicenter RCTs without proper support cannot be reliably performed in studies investigating complex research questions.[13] While clinicians participating in IITs are a select subgroup of investigators willing to renounce the fees generally received from the industry for the advancement of medical and scientific knowledge, their site payment to cover local support should at least be in accordance with the principles of Fair Market Value. Merely throwing money at the problem is unlikely to produce meaningful and sustained changes.[14] While academia invest in the training of PhDs, Postdocs and publication of scientific articles, the episodic nature of grant proposals and the budgetary restrictions do not accommodate infrastructure building. The ad hoc fashion in which IITs are currently being conducted needs to be urgently addressed. Efficiency could be gained by organizing the local clinical research infrastructure so that those exploring new research questions could quickly draw on resources already in place, instead of reinventing the wheel for each trial.[11] The goal should be to allow investigators to focus on their work as clinical researchers, rather than having to serve as project managers, by decreasing their non-scientific burden and to optimize the use of existing clinical research tools. While the initiating hospital received indispensable support from the KUL Research and Development and the Clinical Trial Centre respectively for the legal, contractual and financial management of the project; and the local trial implementation in the associated hospital- a multitude of organizational and administrative tasks are still to be completed by the initiating investigator. Constructive lobbying for the expansion of clinical research infrastructure should be a specific aim of all stakeholders to promote clinical research, in the interest of public health. The BACE trial, for example, showed clear benefits of an inexpensive treatment (azithromycin, an off-patent antibiotic) in an expensive condition (COPD exacerbations). To remain truly independent, however, we agree with a recent claim of the European Biomed Alliance that academia need more attention from national governments and the European Union.[15] In the meantime, investigator-initiated clinical research could benefit from an adaptation of current regulatory and funding policies to allow consideration for trial- and context-specific challenges.

Limitations

The challenges to successfully conducting an IIT are substantial. The challenges mentioned, nor the recommendations made are exhaustive. The manuscript sought to illustrate how IITs are being conducted and to provide insight to allow others to draw lessons upon. We did not elaborate on the steps that will ultimately lead to a change in policy and adoption by health technology assessment bodies for this off-label use of azithromycin. Where pharmaceutical industry can set up post-marketing surveillance and typically fund replication trials, this cannot be done after an investigator-initiated study once

the entire budget is used. Funding agencies are not likely to fund replication trials as reviewers may not find 'replication' an appealing idea for competitive funding. The National Institute of Health (NIH) Replication of Key Clinical Trials Initiative (U01) provides a window of opportunity in the US. Lastly, the challenge of publishing results -discussed in detail by Lindner et al immediately and disseminating the results to a broad audience (which can be done by marketing departments of the pharmaceutical industry) has not been discussed in this paper.[16]

CONCLUSION

Investigator-initiated clinical research has become an increasingly complex environment in which non-scientific burden through regulation and administration is challenging its future existence. While transparency and patient safety are of utmost importance, there is an urgent need to reconsider the demands which are truly needed to support and fund this creative, independent, but also indispensable research field.

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