Vaccine 41 (2023) 7587–7597

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Conducting an Ebola vaccine trial in a remote area of the Democratic Republic of the Congo: Challenges, mitigations, and lessons learned

Ynke Larivière [a,b,1], Trésor Zola Matuvanga [a,b,c,1,*], Gwen Lemey [a,b], Bernard Isekah Osang'ir [a,b], Paul Peter Vermeiren [a,b], Solange Milolo [c], Rachel Meta [c], Primo Kimbulu [c], Emmanuel Esanga [d], Junior Matangila [c], Jean-Pierre Van geertruyden [b], Pierre Van Damme [a], Vivi Maketa [c], Hypolite Muhindo-Mavoko [c], Patrick Mitashi [c]

[a] Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, University of Antwerp, Wilrijk, Belgium
[b] Global Health Institute, Department of Family Medicine and Population Health, University of Antwerp, Wilrijk, Belgium
[c] Tropical Medicine Department, University of Kinshasa, Kinshasa, Democratic Republic of the Congo, The
[d] Division Provinciale de la Santé de la Tshuapa, Democratic Republic of the Congo, The

ARTICLE INFO

Keywords:
Challenges
Mitigations
Vaccine trial
Remote area
Lessons learned
Ebola vaccine

ABSTRACT

Conducting a vaccine trial in a low- and middle-income country (LMIC) can present unique challenges and lessons learned. This Ebola vaccine trial, enrolling 699 healthcare providers and frontliners and jointly set up by the University of Antwerp (Sponsor) and the University of Kinshasa (Principal Investigator (PI)), was conducted in Boende, a remote city in the Democratic Republic of the Congo (DRC), between December 2019 and October 2022 (ClinicalTrials.gov: NCT04186000). While being bound by strict ICH-GCP and international funder regulations, this trial, exemplary for being a public–private partnership, required collaboration between several international stakeholders (e.g., two universities, a pharmaceutical company, and a clinical research organization), local communities and government agencies. Here we address several logistical and administrative challenges, cultural differences, language barriers and regulatory, political, and ethical considerations over the trial's 2.5-year duration, while tailoring and adapting the study to the specific local context.

Lessons learned include the importance of clear communication with participants in all phases of the study, but also within the study team and among different stakeholders. Challenges, mitigations, and lessons learned are presented in nine categories (e.g., safety management; trial documentation, tools, and materials; communication, staff training and community engagement/sensitization; financial and administrative hurdles; and more). Ultimately, to reach the successful end of the vaccine trial in this remote Ebola endemic area in the DRC, careful planning, collaboration, and great flexibility and adaptability was often required from all involved partners. Despite the encountered challenges, the vaccine trial discussed in this paper was able to obtain high participant retention rates (i.e., 92% of participants completed the study). We hope that other international teams aspiring to conduct similar trials in remote areas of LMICs can learn from the way our challenges were addressed, mitigations developed, and lessons were learned.

1. Background

Vaccine trials are crucial in the fight against infectious diseases. They evaluate the safety, tolerability, immunogenicity, and efficacy of candidate vaccines before they are licensed. Hence, vaccine trials should be conducted in populations of different ages, genders, ethnicities, and geographical and environmental contexts. Additionally, it is incremental to evaluate new candidate vaccines in countries where the disease is endemic [1]. Therefore, the University of Antwerp, as sponsor, and the University of Kinshasa (UNIKIN), as Principal Investigator (PI), jointly conducted an Ebola vaccine trial (hereafter referred to as the EBL2007 trial) in Boende, a city located in a remote and Ebola endemic area in the

* Corresponding author at: Department of Tropical Medicine, University of Kinshasa, Avenue Université numéro 1, Commune de Lemba, Kinshasa, Democratic Republic of the Congo, The.
E-mail address: zola.matuvanga@unikin.ac.cd (T.Z. Matuvanga).
[1] These authors contributed equally to this work; joint first authorship.

https://doi.org/10.1016/j.vaccine.2023.11.030
Received 18 September 2023; Received in revised form 14 November 2023; Accepted 14 November 2023
Available online 22 November 2023

Tshuapa province of the Democratic Republic of the Congo (DRC) [2].

In 2014, the DRC's 7th Ebola outbreak took place in the Boende health district [3]. Of the 69 suspected, probable, and confirmed cases, eight cases (12%) were healthcare providers (HCP), seven of whom died (88% case fatality rate) [3,4]. HCP and frontliners represent a high risk group for contracting and spreading the disease [5]. Therefore, the EBL2007 trial enrolled 699 HCP and frontliners (i.e., medical doctors, nurses, midwives, community health care workers, first aid workers, laboratory technicians, health facility cleaners, hygienists, care givers, pharmacist aids, nutritionists and vaccination program aids) working and living in the Boende health district [2,6]. Each participant was vaccinated with the 2-dose heterologous Ad26.ZEBOV, MVA-BN-Filo vaccine regimen, followed by an Ad26.ZEBOV booster dose one or two years after the initial dose (randomization 1:1) [2] (ClinicalTrials.gov; NCT04186000). The first participant was enrolled on December 18, 2019, and the last participant visit took place on October 12, 2022. An extremely high participant retention rate of 92% was achieved by the research team over 2.5 years of follow up.

Conducting trials in remote areas of low- and middle-income countries (LMICs) where infectious diseases like Ebola virus disease (EVD) occur, is challenging [7–10]. We previously described the encountered challenges, mitigations and lessons learned (at both sponsor and PI level) to set up the EBL2007 trial in Boende [11]. As a follow up, we describe here the challenges, mitigations and lessons learned encountered while conducting the trial. To ensure consistency, we maintained the 8 categories where possible or adapted where required. Some categories, specific to the trial conduct, were added (safety and pharmacy management; influence of other infectious diseases; participant's recruitment and follow-up visits). Our main aim is to expand on what was previously published with the experiences and lessons learned from the actual trial implementation and further progress towards its successful completion (Table 1).

2. Challenges, mitigations & lessons learned (Table 1)

2.1. Regulatory, political, and ethical

In agreement with national guidelines on medical research involving humans [12], the National Health Ethics Committee of the DRC (EC-DRC) conducted a 3-day inspection of the EBL2007 trial site in Boende to ensure that ethical standards were respected and all study procedures were conducted according to the approved protocols. Next to this visit, inspectors from the Laboratory Directorate of the DRC Ministry of Health visited both the trial site and the UNIKIN's cold chain facilities in Kinshasa to verify that the collection, processing, and storage conditions of clinical trial samples followed good clinical & laboratory practices (GCLP), before authorizing the shipment of the samples to laboratories outside the DRC. These visits were expected to be financially supported by the PI, an unexpected responsibility which was thus unforeseen in the budget planning. As pointed out by Kass et al. (2007), funding of EC activities in Africa is generally experiencing significant bottlenecks [13]. Adequate, transparent, and sustainable funding is essential for the effective functioning of an EC, to ensure its independence, and to avoid potential conflicts of interest with investigators.

Despite its challenges, conducting the EBL2007 trial in an Ebola endemic area was relevant and important. Firstly, it was pertinent that the investigational product (IP) was evaluated in a high-risk area. Secondly, participating HCP were likely to be better protected and show clinical efficacy, should an outbreak occur. However, to avoid evaluation bias, hired study staff were not allowed to participate in the study, limiting their own protection against a possible Ebola infection. Consequently, while the risks initially seemed low, several mitigations and measures had to be in place to adequately support and protect study staff (e.g., training national and international staff on sanitation and safety precautions, liaising with local and national public health authorities) and when the trial was ongoing, a suspected (but eventually

Table 1
Encountered challenges, mitigations and lessons learned during the conduct of an Ebola vaccine trial in Boende, Tshuapa province, DRC.

#	Challenges	Mitigations	Lessons learned
1	Regulatory, political, and ethical		
	Financially support unforeseen regulatory and ethical institutions' visit requests to inspect the study site.	The study budget was reshuffled to allow the site visit of the regulatory and ethical institutions, at their request. The principal investigator (PI) ensured his presence at the site when the visit occurred.	Keep in mind unforeseen (organizational and budgetary) requests from regulatory and ethical institutions. Include a buffer for risk mitigation or contingencies in the trial budget.
	Unvaccinated study staff against Ebola virus disease, working in an Ebola endemic area.	Not applicable.	Depending on the disease, the availability of vaccines and the trial design, vaccination of study staff should be considered either at onset of the trial or as a post-trial measure.
	Trial participants suffered from (serious) adverse events throughout the trial, but the local healthcare system was dysfunctional and operates largely on out-of-pocket contributions.	Provision on ancillary care via the development of a *(non-)related (serious) adverse event ((N)R-(S)AE) algorithm and policy* for participants for the duration of the trial.	Algorithms and policies can help guide the PI and local staff on financial and medical ancillary care decision making and management.
2	Trial documents, tools, and material		
	Archiving source documents by the principal investigator (e.g. case report forms (CRFs), informed consent forms (ICFs), etc.) between Boende (site location) and Kinshasa (headquarters PI).	A storage method/ system was developed using the study visit and subject identification number, so that information remained coded. A travel plan was developed together with the sponsor in which it was determined which documents were needed at the site before each active period started.	Develop an archiving system for study documents before the start-up of the study. Develop a list of the documents needed per visit. Develop a travel plan and ensure timely shipment of the required documents to and from the site.
	The design of the CRFs information such as the dates of form completion or clinical visits.	Source document notes were utilized to gather the missing dates of study visits.	Always ensure that all information is recorded, with specific attention to dates. Clinical notes, next to the CRF can be essential to document all information/ performed actions, as they may be needed for reference in the future.If data is not collected electronically (with a time stamp of completion) but on paper, ensure that each source document and CRF page has the date of the performed action.
	Identifying treatment and trial disposition dates for participants that did not	*Treatment and trial disposition algorithms* were developed by the sponsor to help	Algorithms can be useful tools to create clarity in complex situations.

(*continued on next page*)

Table 1 (*continued*)

#	Challenges	Mitigations	Lessons learned
	complete the study (e.g. lost to follow-up, moved, etc.).	the PI and monitors remain consistent when identifying treatment and trial end dates.	
	High numbers of (severe) arterial hypertension in enrolled study participants.	The sponsor and PI developed *hypertension algorithms* that helped guide study doctors on what to do/how to treat participants with (severe) hypertension during a study visit where participants were supposed to be vaccinated.	Algorithms can be useful tools to help guide local staff during vaccination visits. Identify a referral hospital/treatment centre where participants with severe arterial hypertension can go after being diagnosed.
	GCP compliance - Storage of thousands of study documents for 25 years.	Digitization of the source documents: • Source documents containing personal information (e.g. ICF) was stored by the PI. • All other documents were digitized by the sponsor using a specialized company. Digitized documents were stored on two password protected hard drives. One for the sponsor and one for the PI. This set-up was reported in a note to file to the investigator site file and the trial master file of the study.	Ensure digitization of the source documents to prevent humidity and long-term storage challenges.If digitization is not possible, ensure a large enough storage area with dehumidifiers and humidistat (to regulate the humidity) in tropical climates.
	Axillary temperature measurement led to impossible temperature measurements results among some participants.	The recorded temperature measurements in participant adverse event diaries that seemed medically impossible (e.g., hypothermic measurements) were discussed by the study medical doctor with the participant during a reactogenicity assessment. A medical decision by the medical doctor was then made to determine whether a participant was truly hypothermic based on clinical assessment and interrogation.	Always ensure clear explanations to the participant on how to conduct study related activities.Foresee oral temperature measurements (instead of axillary temperature measurements) to minimize measurement bias when possible. After ensuring clear explanations of the required study activity, verify whether oral temperature measurements are culturally accepted. Perform a pilot study if necessary.Re-test calibrated material (e.g., thermometer) together with the participant before sending the participant home with the thermometer.
	Terminology that is usually used, was not applicable in the study population.	Erythema (redness) that had more of a brown discoloration after vaccination at the injection site than a red discoloration was not always considered as erythema by some of the participants. Reactogenicity assessment of the medical doctor was required to identify those participants that did have erythema but did not report it as such.	Ensure that the medical jargon used is applicable for your study population.
3	Safety and pharmacy management		
	Difficulty to report some SAEs to the sponsor within the required 24 h after becoming aware of the SAE.	If delays in SAE reporting were expected (later than 24 h after becoming aware), the PI informed the sponsor of this via WhatsApp. This allowed the sponsor team to be aware that an SAE report would be shared by the PI as soon as possible.	Think about the use of social media (e.g., Whatsapp) to improve the speed of the necessary initial communication between the PI and sponsor, pharmaceutical company, etc.
	Impossible to fully rely on the hospital pharmacy (or other external pharmacies)	An adapted version of the World Health Organization (WHO) *Interagency Emergency kit Health Kit* was used as basis for a study pharmacy construction but had to be adapted throughout the trial to consider the most common pathologies in the area.	Provision of a study pharmacy was essential. The WHO *Model List of Essential Medicines* can be a good starting point. Good contact with the local health authorities and pharmacies can assist in adjusting the list of medications needed, before the start of the trial. Adapting the pharmacy to the local research context, trial population and usages throughout the trial can be achieved with the help of and connections with local health authorities.
4	Communication, staff training and community engagement/sensitization		
	Long passive study periods within a > 2.5-year study duration.	Study staff was retrained prior to each active study phase on applicable study procedures, protocol amendments, ICF amendments, etc. Participants were invited for workshops on the eve prior to each study visit. Workshops included sessions on the trial activities and basic and more advanced medicine.A	Re-inform trial participants and staff about the trial study procedures before each active study stage (i.e., what will happen during the next few visits). If a long study duration applies, use this opportunity to train local health care providers through workshops.

(*continued on next page*)

Table 1 (*continued*)

#	Challenges	Mitigations	Lessons learned
		test of understanding (TOU) was performed yearly, before each active study stage, to assess the knowledge of study participants on the conduct of the trial.	
	Attempt of study participation fraud.	Iris scanning was used to identify members of the community that pretended to be a participant.	Use biometric identifications tools to help identify attempts of fraud that would otherwise be missed.
	A yellow fever vaccination campaign in Boende led to a vaccine related death.	Prior to starting the trial, community health care providers (*relais communautaire*) were trained by social science professors from UNIKIN to help distribute correct information to communities during the conduct of the trial. Additionally, participants were invited for a workshops 24 h before each study visit. During this workshop, the PI took the opportunity to respond to any questions, rumors, and uncertainties regarding the study vaccines.	Continued and clear communicating with the community throughout the conduct of a trial can be challenging. By training local community HCP before the start-up of the trial, rumors and uncertainties in the community can be timely addressed while conducting the trial.Be alert to what is ongoing in the trial surroundings and anticipate and mitigate dropouts before they happen.
	Participants indicated on several occasions to want to know the outcome of this study and their contribution to it.	Sponsor and PI are organizing a dissemination conference in Boende for study participants, local health authorities, national EC-members, and international stakeholders once all trial results are available.	Foresee a communication channel to distribute study results to the participants and other relevant parties.
5	Participant's recruitment and follow-up visits		
	Complaints from some participants about the length of time they had to stand by while being screened, consented, bled and vaccinated.	Staff debriefing by the site coordinator on a daily basis. Readjustment of the participants flow initially designed to accommodate and improve the participants' mobility within the study site during screening and follow up visits.	For better preparation and scheduling of each participant visit, provide notice of the estimated duration of the screening and participant inclusion process and other follow-up visits to the participants.
	Participants residing in area without network coverage.	Obtain information on how to reach participants and remind them of upcoming study visits before a visit window was about to be exceeded.Prompt (or real-time) notification to the PI or study site of the occurrence of a problem with safety.	The cooperation of the local health committee is a key factor in optimizing enrolment and follow-up within a trial in a remote area.
	One year after the start of the trial, recruited first aid worker coordination members wanted to be compensated in terms of equipment, operating funds, etc.	First aid worker members were invited to contribute to the community engagement and capacity building strategy of the study.	Be alert for any rumors and anticipate and mitigate conflicts before they happen.
6	Remoteness and climate conditions		
	Changed flight schedules; Multiple plane crashes in the East; Weather condition hindering flights.	A plane was chartered with a trustworthy airline if vaccines needed to be transported to Boende site or if enough staff had to fly as it was safer than flying with the local airline.	Always assess the safety of the staff that is flying to remote study sites and develop a risk benefit assessment of each airline. Ensure flexibility of study staff in remote locations with uncertain weather conditions. Foresee enough time between domestic flights and international flights, when applicable.
	Internet connectivity issues	The PI often switched providers based on cost-efficacy.To avoid data collection delays, a local server was set up that transmitted the data to a central server as soon as internet connectivity was available.	Know available providers in the study area and make a cost-effectiveness evaluation prior to starting the study. Set up a local server that transmits data when internet is available, if possible.
	Damaged generators and unavailability of high-quality fuel in Boende for generators	Despite having several generators (back-ups of each other), this method of foreseeing electricity was not fully reliable. An expert in repairing generators was sought in Kinshasa and had to fly to Boende to repair damaged generators. High quality fuel was shipped from Kinshasa to Boende to ensure the generators would run smoothly.	Mitigations to avoid low-quality fuel in such a setting were difficult to establish. Local capacity building on all levels may be required to ensure a smooth continuation of the study trial. Foresee budgetary implications for repair and capacity building in remote study locations. Alternative energy sources to generators (e.g., solar energy) should be explored when setting up a study in a remote location.
7	Influence of other infectious diseases		
	Ebola outbreak in Mbandaka	The protocol contained a section on next steps in case of an Ebola epidemic in the study area.	Always be alert for a new outbreak when conducting research in an endemic area. Foresee a contingency plan in the event an epidemic occurs in the study area.
	COVID-19 Pandemic and Site implications: • Travel ban in DRC.	Travel ban: The network of the PI was used to obtain a plane to Kinshasa at the end	Try to establish a good relationship with political authorities. Foresee a

(*continued on next page*)

Table 1 (*continued*)

#	Challenges	Mitigations	Lessons learned
	• Power supply fail mid-covid. • Rumors on mix-up between Ebola booster dose and COVID-19 vaccine. • Sample shipment analysis delayed. • Worldwide stock ruptures in laboratory material and medical consumables. • Sponsor staff unable to travel to DRC for support (international travel ban). • Monitors unable to travel to the site. • Longer sponsor travel visits required after travel ban removal because of testing and quarantine. • Additional cost of testing to travel to site (UNIKIN)/DRC and site (sponsor).	of the first active study period (during the national lockdown period). Power supply: expanded program on immunization generators were used as back-up. Rumors: When COVID-19 occurred, rumors were addressed during workshops, for which participant were invited 24 h prior to their study visit. Impossibility to order certain required laboratory material: The University of Antwerp network was used to obtain the necessary material. Delay in sample shipment: Readiness of samples and courier were ensured as soon as borders opened up, and air transport was possible. Cancelled sponsor visit: Continuous online contact between site, PI and sponsor was ensured and the sponsor tried to help remotely where possible. Cancelled monitor visit: Monitoring visits was delayed until it was possible to perform the monitoring at PI headquarters in Kinshasa. Additional costs: Pay the additional costs for testing and plan longer study visits to include quarantine days.	resilient contingency plan and travel plan (for staff, samples, and source documents). Taylor community engagement to include unexpected events that could have an impact on participant perception of the trial. Flexibility from all parties is required and a solution driven approach should be practiced when coming across unexpected situations.Foresee a buffer in study budgets for unforeseen additional expenses (e.g., Covid testing, longer research stays due to quarantine) .
8	(Inter)national collaborations		
	Large staff turnover in some teams.	Turnover documents were developed to ensure adequate information was passed on to a successor. The sponsor team ensured that each staff member had a back-up within the team. This way, no issues were left unaddressed when someone went on holiday for example.	Ensure clear communication, plans and SOPs for a smooth continuation of the study during high staff turnover. Develop turnover documents to ensure the most important details are passed on to successors. Foresee trained back-up personnel in each team.
	Data coding responsibilities and discussions.	Many meetings were needed to discover the reason for inconsistencies in expectations concerning coding of the data.	Ensure clear communication, including clear guidelines on which software versions to use and expectations of each involved institution.
	Medical writer selection.	The required budget was higher than initially foreseen. Three companies had to be contacted according to Belgian law.	When subcontracting, check the requirements of the funder before approaching companies. Involve your institute's processing department before approaching qualified companies if budget implications are unknown.
	Language barrier.	On site, translators were hired when required. Some of the study team members spoke the necessary languages and could function as translators during meetings.	If possible, hire local staff that speak the necessary languages. If this is not possible for the established international collaborations, ensure that some of the staff in the sponsor and PI team can function as translators.
	Delay in sample analysis: • Covid-19. • Moving locations of laboratory: FDA approval required after moving; no sample results could be shared until approval was obtained.	The sponsor ensured frequent communication and meetings with the pharmaceutical company and the analyzing lab to discuss progress and potential solutions to delays.	When funding lasts for a certain amount of time, ensure enough wrap-up time or potential delays before funding is scheduled to end. If not, keep in mind that a no cost extension request with the funder may be required.
9	Financial and administrative hurdles		
	Funders' reporting requirements can burden the capacity of partners' administrations in LMIC.	Sponsor's administrators provided close follow up and capacity training for the partners and collaborated with the financial teams (Boende and Kinshasa) in the field to develop a project-specific accounting system.	The partners' administrative coordinators should to be involved from the initial set up of the project in order to develop an adapted project reporting system that enables a smooth operational roll out, while simultaneously adhering to the funders' binding guidelines.
	Differences between the administrative set up of the funder and financial auditors and the local reality and practices in LMIC can lead to financial uncertainties and delays in funding.	Consortium coordinator and partners cooperated closely by unifying the experience and know-how of audits in order to find solutions to the funder's and auditor's requests.	Consortium partners are advised to exchange their experiences and know-how of audits conducted in projects in LMICs. The most experienced partners in the consortium should provide support to others for the benefit of the project as a whole.
	Funder-designed processes can be bureaucratic when correcting flaws or amending research activities in consortium set up.	Lengthy, recurrent exchanges and discussions between funder, consortium coordinator and involved partners, with frequent references to initial	Enable a sound financial and administrative set up of the research consortium at the project's proposal stage by involving the

(*continued on next page*)

Table 1 (*continued*)

#	Challenges	Mitigations	Lessons learned
		proposals and contract clauses.	administrative project coordinators.
	Running a project using three different currencies in a cash-reliant country.	Very close follow up of the cash movements by means of the cash ledger and monitoring of the exchange rate risks.	Encourage a disciplined use of the cash ledger and a close cooperation with the financial administrators is paramount in controlling the substantial cash movements within the project.

not confirmed) Ebola case was reported near the study area. Therefore, depending on the disease, the availability of vaccines and the trial design, vaccination of study staff should be considered either at onset of the trial or as a post-trial measure.

In remote and resource-constrained areas in LMICs, access to quality healthcare may be challenging. However, when quality healthcare is inadequate, legislation or binding regulations require sponsors to provide care to conditions unrelated to the IP, also referred to as Ancillary Care (AC) [14,15]. Hence, our research team developed a policy, combined with a decision algorithm, to systematically and non-arbitrarily approach and support participants' concomitant medical events [16]. The development and modalities of this specific AC approach, as well as its implementation challenges, are described elsewhere [16,17].

2.2. Trial documents, tools, and material

Since the PI was based in Kinshasa, the capital city of the DRC and approximately a 3h30min flight from the trial site in Boende, the archiving of paper source documents (e.g., informed consent forms (ICFs), case report forms (CRFs), logs) came with its unique challenges. General lessons included; (1) the necessity to have a predefined travel plan to keep track of source document mobility; (2) due to rodents and weather conditions, high level documents such as ICFs are best stored in a safe or lockable cupboards; (3) documents are best filed by participant ID so that records can be easily identified when needed (this study stored source documents per visit and document type); (4) the study visit date should be reported on each source document and CRF page, as this may be crucial to reconstruct a participant's study timeline when assessing treatment and trial disposition timelines during analysis; (5) algorithms can provide guidance (e.g., AC algorithm and policy; how to identify reasons and dates for treatment/trial disposition; etc.). Though algorithms/guidelines offer a framework, they should not replace rational thinking and decision-making for each individual case.

As the vaccine trial was conducted under the Innovative Medicines Initiative (IMI), which is a European Union (EU) public–private partnership, it had to abide by EU pharmaceutical legislation [18]. While this legislation indicates that medical records of participants must be archived in compliance with national law [19], the storage duration mandated by the DRC law is unclear. For this reason, the research team (consisting of sponsor and PI) decided that all source documentation would be stored for the same duration as the trial master file, which follows EU legislation, and amounts to 25 years [19]. To achieve long-term storage without the constraints of weather or storage limitations, all paper source documents without patient identifiers were digitized. The digital source documents replaced the paper versions, with the approval of the EC-DRC. The Good Clinical Practice (GCP) guidelines (ICH E6, 4.9) further highlight the importance for the archiving system to enable document identification, version history, search, and retrieval [20]. To allow anyone to find a specific term within a PDF, the documents contained optical character recognition. After digitization and quality checks, the source documents were destroyed by the digitization company. The sponsor and PI are both in possession of a password protected hard drive, on which the digitized source documents are stored. Only delegated staff within both institutions have access to the password. The PI stored documents with patient identifiers (e.g., ICFs) elsewhere.

Culturally accepted practices need to be taken into consideration when developing documents and determining procedures to be carried out during a trial. In this study, axillary temperature measurements were taken. The PI determined that the use of axillary temperature measurement would be culturally acceptable as it is a globally recognized non-invasive standard, although it may be less accurate and precise than oral measurements [21]. However, discrepancies were noted among some study participants who recorded hypothermic readings below 35.0 °C, which were later invalidated by the study physician's reactogenicity assessment, attributing them to improper axillary thermometer usage. While several mitigations were taken to prevent inaccurate axillary temperature measurements (i.e., provision of a personal thermometer per participant and providing clear instructions on its proper use), such inaccuracies still occurred. Consequently, we posit that oral temperature assessment might be less prone to user error and thus more reliable than axillary methods.

Furthermore, when creating trial documents, it is crucial to consider the overall appearance of potential study participants. In this trial, solicited adverse event terminology was included in the participant journal as it had been used in previous studies assessing the safety of the vaccines. One of the symptoms documented was *erythema* (described as redness of the skin in journal guidelines). However, after booster vaccination some participants did not report any *redness* at the injection site in their participant journal. Yet, when questioned during a follow-up visit, they reported a more *brown* discoloration at the injection site instead. Hence, they did not measure this discoloration because it was not really *red* as described in the guidelines and as elucidated to study participants. Therefore, we recommend ensuring that the assessed (medical) symptom terminology and guidelines apply to the study population being assessed and to adapt terminology and guidelines accordingly, if required.

2.3. Safety management

Since the trial was conducted in a remote area with frequent disruptions in mobile network communication and in internet connection used at the study site, there was significant risk of a delay (more than 24 h) in reporting serious adverse events (SAEs). To anticipate this, the SOP for SAE reporting allowed the sponsor to be informed via WhatsApp before a more detailed report followed. In addition, to prevent any missing SAEs, participants were informed at the beginning of the study that a toll-free number was available to contact the site. Health facility managers (Nurse Attendants) were also asked to notify the study site coordinator upon receiving a study participant with a health problem at their health facility. This was particularly important for participants residing outside of the mobile phone network range (10 km radius from the trial site; Fig. 1).

To temporarily improve the availability of basic healthcare for trial participants, a study pharmacy was foreseen to provide AC. This pharmacy was set up using the *Interagency Emergency Health Kit* of the World Health Organization as a starting point [22]. However, not all medication and supplies were relevant nor included to provide basic healthcare to the study participants. Therefore, adaptations in medications and amounts were made before the trial started and were refilled based on consumption as the trial progressed. In hindsight, while the emergency health kit served as a worthwhile starting point, the *Model List of Essential Medicines* may have been more applicable as this list includes the minimum medication requirements to deliver primary healthcare [23].

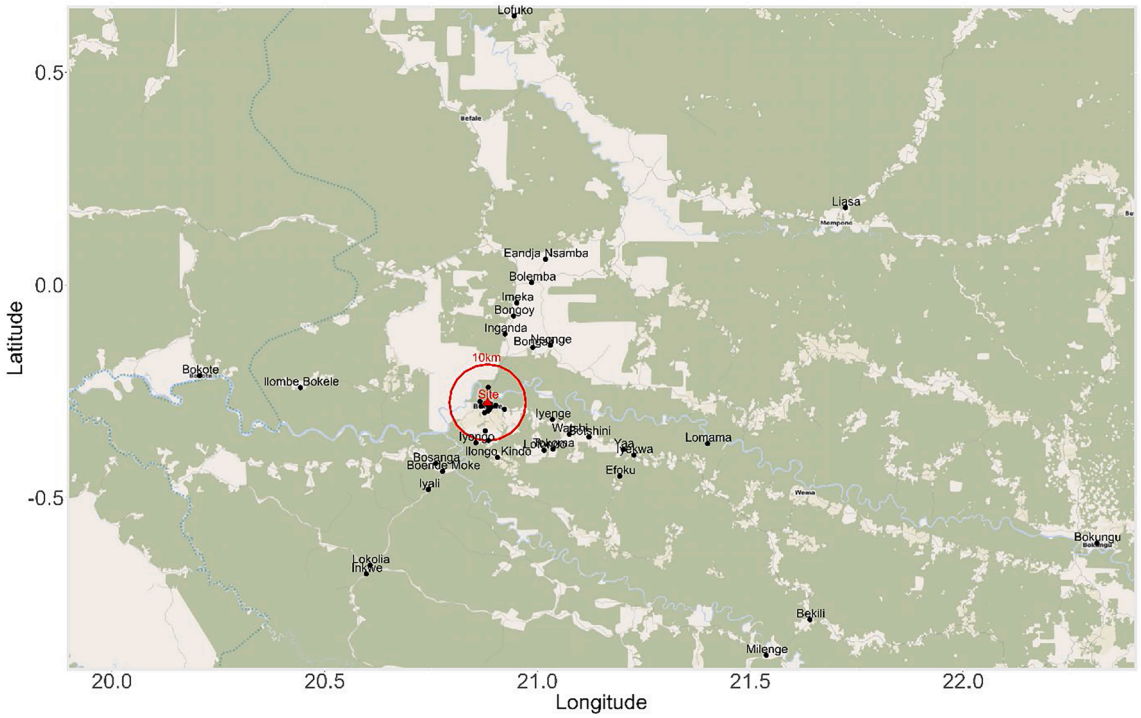

Fig. 1. Mobile phone network range around Boende The site location in Boende is shown in a red triangle, the 10 km mobile phone network radius is indicated with a red circle. Participants living in villages outside of this red circle, could not be contacted via mobile phone. Villages of participants' residence outside the 10 km radius are indicated with a black dot and the village name. The map was made in R version 4.3.1 and is presented as type osm-public-transport. The circle was added using the packages rgeos and sp. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.4. Communication, staff training and community engagement/ sensitization

The EBL2007 trial had long intermittent study periods where no active study visits took place. In total, the trial was split into three stages (Fig. 2). While long passive periods were essentially not a problem, retraining study staff on the protocol, GCP, SOPs, etc. was essential before the start of each active study stage. Each year the training courses were updated to include the necessary procedures according to the upcoming study visit and were taught by clinical research associations, the sponsor-team and the PI-team.

In line with retraining staff after long passive periods, we found that it was important to (re)explain the upcoming study activities and ICF content to trial participants prior to their next study visit. This was learned through a test of understanding collected prior to enrollment and before each active study period. To maximize understanding of the trial, capacity-building workshops were held on the eve of the screening and recruitment day and all other follow-up visits scheduled in the trial. These capacity-building workshops with participating HCP, covered educational topics on non-medical preventive measures against EVD or other diseases or health issues, coupled with explanatory sessions and necessary information related to the conduct of the clinical trial. This

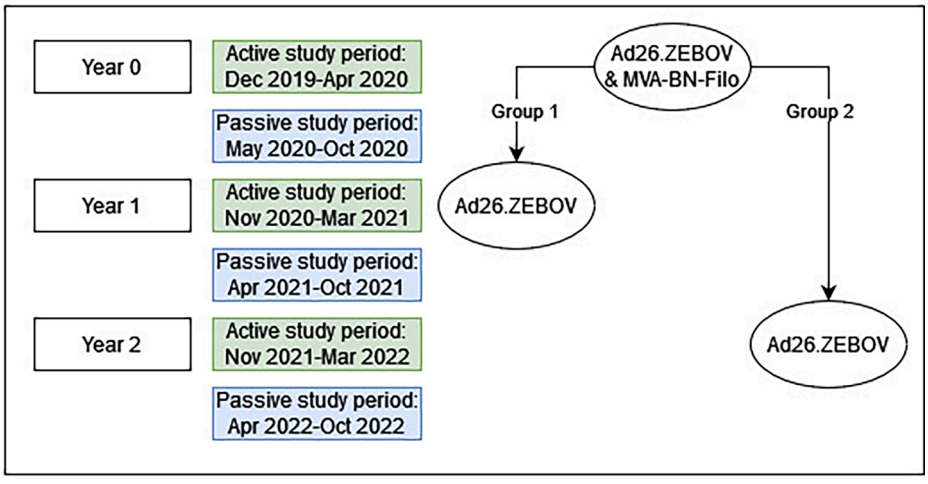

Fig. 2. Simplistic overview of the EBL2007 Ebola vaccine trial The EBL2007 trial can by split up into active (green) and passive (blue) stages. During active stages, vaccination, blood sample collection and safety assessments took place during scheduled visits. In passive stages, serious adverse events were collected during unscheduled visits or scheduled phone call visits. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was followed by a question-and-answer session to address any questions or concerns of participants.

Because the study vaccine regimen was to be administered in two doses, followed by a booster (Fig. 2), it was imperative to ensure that the correct individual was vaccinated. For this reason, an iris scan tool was used throughout the trial to ensure correct identification of participants [24]. The iris scans were captured on tablets and transferred to a portable server via local Wi-Fi. Iris scans were recorded in a binary code and the code was encrypted in rest and transit from the tablet to the portable server. These encrypted data were backed up on an external hard drive daily. Both the portable server and hard drive were stored securely at the study site. Access to the main server and back-up hard drive was restricted to designated trial staff, ensuring participant identity protection. Incidents of fraud were detected by this scanning tool when family members tried to present themselves as a substitute for participants who were unable to attend a scheduled visit at the clinical trial site. Therefore, biometric identification should be considered for longitudinal studies.

Other challenges were encountered during a yellow fever preventive vaccination campaign when a yellow fever-vaccine related death (classified by the pharmacovigilance center) took place in the Boende health district. This occurred between the heterologous two-dose vaccine regimen and the booster dose (Ad26.ZEBOV) administrations at Year 1 (Fig. 2). Interestingly, this incident did not have an impact on the EBL2007 vaccine retention rates. We formulated three hypotheses for this observation. First, we enrolled HCP, a (relatively) well-educated population who was able to discern that the study vaccines used were different from the yellow fever vaccine. Second, capacity-building workshops and sensitization sessions between the communication task force and participants on the eve of each scheduled visit built participant confidence and anticipated the spread of false messages or rumors. Third, with the 2014 Ebola outbreak in mind, participants considered the risks of Ebola vaccines acceptable.

Finally, in the spirit of open communication and community engagement, the sponsor and PI team found it important to communicate to the participants, local health authorities and the EC-DRC what the outcomes of the trial are. For this reason, a face-to-face dissemination conference is planned in Boende when all study results are available and analyzed. The conference planning is ongoing at the time of this writing. This step, though ethically relevant and often important to participants, is often omitted in scientific research.

2.5. Participant's recruitment and follow-up visits

During the initial enrollment visits, participants spent an average of 2 h at the trial site. This time was eventually reduced to less than 45 min per participant through morning briefing sessions, and staff experience. To avoid complaints, we recommend warning participants about the duration of the screening and enrolment processes so they can prepare and schedule their work activities on that day. Additionally, morning briefing sessions between study staff and the site coordinator are important to discuss difficulties encountered on previous days, so solutions can be sought.

Several trial participants lived in villages beyond the mobile network coverage in the Boende health district (Fig. 1). Their only means of accessing the site was on foot, by bicycle, with dugout canoes or by motorcycle. This presented a challenge in terms of localizing and/or reminding participants of upcoming study visits. To minimize the loss of follow-up of these participants and to maximize their comfort and well-being throughout the trial, the PI reimbursed travel expenses for all participants and additional accommodation and meal expenses for any participants travelling more than 6 h (approximately >25 km) to the trial site. Additional reminders were made through the health district's community health workers (identified at the beginning of the trial) to locate participants who did not attend scheduled study visits.

At the very beginning, first aid workers of the Boende health district were contacted to participate in the EBL2007 trial, given their status as stakeholders in the process of safe burial during Ebola epidemics. A meeting was held with the first aid worker coordination team, to explain the main objectives and procedure of the study and to compile a list of potential study participants. When starting recruitment, several members agreed to participate in the study and very good adherence to the various appointments was noted. However, at the start of the Year 1 visits (Fig. 2), the coordination team of first aid workers contacted the PI and asked to be compensated in terms of equipment, operating funds, etc. As it would be unethical to compensate institutions for their members to participate, the PI could not respond to these requests. Consequently, the coordination team countered by suggesting all first aid worker participants leave the study. After lengthy discussions, a solution was found; some coordination team members would be hired to give capacity building workshops planned in the study. This experience demonstrates that unexpected circumstances can arise, and that flexible and at times creative solutions need to be sought to maximally avoid dropout rates from escalating.

2.6. Remoteness and climate conditions

Boende can be accessed from Kinshasa either by river, which can take up to two weeks using makeshift boats transporting goods along the Congo River, or by air, which takes approximately 1h45min to 3h30min depending on the type of plane and airline company. However, considering the high risks associated with the river routes, domestic flights to Boende - operated by two commercial airlines (limited to one flight per week) - are in high demand. Unfortunately, flight cancellations can occur due to weather conditions (e.g., heavy rain, strong winds), technical issues (e.g., maintenance failures, lack of kerosene, failure to confirm the flight 24 h in advance) or unavailability of the aircraft (e.g., leased to officials for travel within the DRC). A well-designed travel plan, and collaboration with charter companies for personnel transportation, vaccine delivery, and sample shipment, helped mitigate the negative impact of these constraints.

In terms of high-speed internet access, the DRC as a whole lags behind [25]. Access to a submarine cable system is limited to a few areas (primarily concentrated in major cities), but is non-existent in Boende. Furthermore, mobile internet access in Boende is extremely limited and more complex compared to Kinshasa. A thorough understanding of the internet provider landscape, enabling better planning and minimizing potential disruptions in the continuity of the study was important. However, while some suppliers offered good services at the beginning of their contract, this often declined over time and new solutions/providers had to be sought. For data collection, the limited internet connection was resolved through the setup of a DFdiscover local server, on which data entry took place. Data were copied over from the local server to the central server on a daily basis as connectivity permitted using a satellite uplink. Both servers were fully 21 CFR Part 11 compliant.

Three generators operated daily, with a shift change every 12 h to foresee the study site of electricity. Despite these arrangements, several breakdowns occurred during trial activities (e.g., because of lightning strikes or bad quality of local fuel). Therefore, high quality fuel had to be imported from Mbandaka (Equateur Province) to Boende. Furthermore, the lack of technical expertise in Boende for generator maintenance and upkeep posed a challenge. The PI had to subcontract a company from Kinshasa for regular maintenance missions to Boende. In hindsight, it might have been more advantageous to have a solar power source as a backup to the generators. Having a solar power source would have provided a reliable and sustainable alternative energy option, ensuring an uninterrupted power supply and reducing dependence on external resources in critical situations.

2.7. Influence of other infectious diseases

During the EBL2007 trial in Boende, a total of six outbreaks of EVD

occurred in the DRC. These outbreaks alternated between two provinces (North Kivu and Equateur). While no Ebola outbreak was officially declared in the Boende area, Mbandaka has a robust commercial connection with Boende via the river. Additionally, the index case of the DRC's 14th outbreak in Mbandaka had returned from a medical internship at the GRH in Boende, where the trial site was located. These outbreaks and the strong connection between Boende and Mbandaka, likely led to a heightened perception of the risk of EVD occurrence in Boende, motivating the study population to accept the investigational vaccine.

Seen the overabundance of (mis)information and related vaccine-hesitancy during the global COVID-19 pandemic, there was a very negative perception of COVID-19 vaccines and their deployment in the DRC, which faced numerous challenges [26]. Some HCP participants in the EBL2007 trial were convinced that the deployment of COVID-19 vaccines was unnecessary in Boende. Their perception was influenced by several factors, including a perceived low-risk of the pandemic due to the absence of reported cases in the region until a year after the pandemic began, and the erroneous belief/misconception that having received the study's Ebola vaccine would provide sufficient protection against COVID-19.

The first COVID-19 case in the DRC was reported in March 2020 in Kinshasa, four months after the start of the EBL2007 trial. Unfortunately, this period coincided with active participant visits at the study site in Boende (Fig. 2) and the containment measures of the public health emergency decree, issued in the DRC, banned national and international flights and national transport by boat with passengers. This emergency status complicated logistical support to the clinical trial staff in Boende; cash transfers could not come from Kinshasa (no bank exists in Boende), serum samples could not be shipped to the destined laboratories and the supporting trial staff from UNIKIN, Kinshasa, was grounded in Boende. However, thanks to the support of the Provincial Health Division on the one hand, and the connections of the PI with relevant national political and administrative authorities on the other, the local team was able to ensure the continuity of trial activities. Fortunately, Boende being very remote, the site and study activities were only slightly affected by the pandemic. Only one participant missed his/her study visit because of the national travel ban whereby the participant could not return from travels for a scheduled visit. Once trial activities terminated during national lockdowns, the UNIKIN staff working in Boende and the collected samples were exceptionally able to return to Kinshasa by means of a chartered flight that had received special authorization from the political-administrative authorities of DRC.

Unfortunately, once the samples reached Kinshasa, these could not be sent on to the international laboratory for testing until the international flight ban was lifted and the backlog of cargo flights was resolved. While sample collection for the first active period ended on the April 25, 2020, the samples could not be shipped to the United States (San Juan Capistrano, CA) until October 31, 2020. Additionally, the capacity to analyze samples was further delayed due to lock downs and diminished staffing availability in the laboratory as well as the prioritization of COVID-19 testing. Therefore, final sample results were not obtained until January 28, 2022.

Another consequence of the lockdowns and flight restriction was the impossibility for others to reach the site location. Support and trainings from the sponsor that was foreseen on site, had to be cancelled and given online. Additionally, monitors could not reach the site and remote monitoring methods had to be set up.

Once lockdowns had lifted and travelling was possible again, new challenges arose. Negative COVID-19 PCR tests were required prior to both domestic and international travels, leading to unforeseen costs and travel time, as a quarantine period in Kinshasa before leaving for and after returning from Boende was obligatory.

When preparing for the active study period in Year 1 in August-October 2021 (Fig. 2), COVID-19 was still in full swing. Factories making laboratory and medical equipment/material had to go into lockdown or were brought down to limited staffing, leading to limited stock availability. The world's available stock had been redirected to fight the pandemic and to COVID-19 related research, impacting other ongoing research. For example, between August-October 2021, cryotubes were impossible to find on the market. In the end, this could only be resolved by obtaining excess stock from other studies of other research teams within the University of Antwerp. Luckily, this allowed the EBL2007 trial to continue as planned.

Once trial activities resumed for the second active phase (Year 1, Fig. 2), preventive public health measures were incorporated into the trial activities. These included reducing the number of participants at the site, mandatory wearing of masks by all staff and participants, and the wearing of protective face visors and lab coats by laboratory personnel. This was based on an update of the biosafety SOP in relation to COVID-19. Furthermore, a negative COVID-19 test was required for anyone travelling from outside of the Tshuapa province. Some additional precautions were taken within the trial team, including the requirement that study staff with COVID-19 symptoms refrain from coming to the site, and consult the health services in Boende for diagnosis and appropriate management. Finally, once possible, COVID-19 self-tests were made available for participants or staff presenting with symptoms. In total, five participants tested positive during the trial. However, no participants experienced severe symptoms or hospitalization as consequence of a COVID-19 infection.

2.8. *(Inter)national collaborations*

With many international teams involved directly or indirectly in the EBL2007 trial activities (Fig. 3), several challenges and difficulties were encountered. First, some teams had large staff turnovers throughout the trial, at times making it difficult to ensure continuity for other partners. Second, though roles and responsibilities were clearly defined in a project management plan at the beginning of the trial, the study and the teams evolved. In doing so, the clearly allocated roles and responsibilities sometimes became blurry. In a project that lasts several years, we therefore recommend reassessing, redefine and reassign these roles and responsibilities at predefined time points or more frequently when needed. Thirdly, while the main language used in the consortium and among partners was English, the local languages in Boende were French and Lingala. Language differences and barriers needed to be considered when developing study material that reached the study staff and participants or when hiring staff that worked in these different language environments. Finally, the most important aspect of working with such many partners was clear and frequent communication, to avoid misunderstandings. This was ensured through daily, weekly, or monthly meetings (depending on the need) between the relevant partners and stakeholders. For example, within the EBL2007 trial, weekly meetings within the sponsor team but also between the sponsor and the PI teams; the sponsor and pharmaceutical company; the sponsor, PI, and data management company; and the sponsor and the clinical research organization were held.

2.9. *Financial and administrative hurdles*

Conducting research projects in resource-poor LMICs, with two financial chairs (e.g., one in Boende and one in Kinshasa) was challenging. Adhering at the same time to elaborate and binding funder's financial and administrative guidelines added additional challenges for the PI's administrations.

Funders and financial auditors, based in Europe or other 'Western' high income countries, tend to draft agreements and guidelines based on their own - often complex - administrative and financial practices. However, these agreements and practices do not always consider the local realities, legal situation, or usual accounting practices of the reporting entities in LMICs. For the PI to abide by these guidelines and

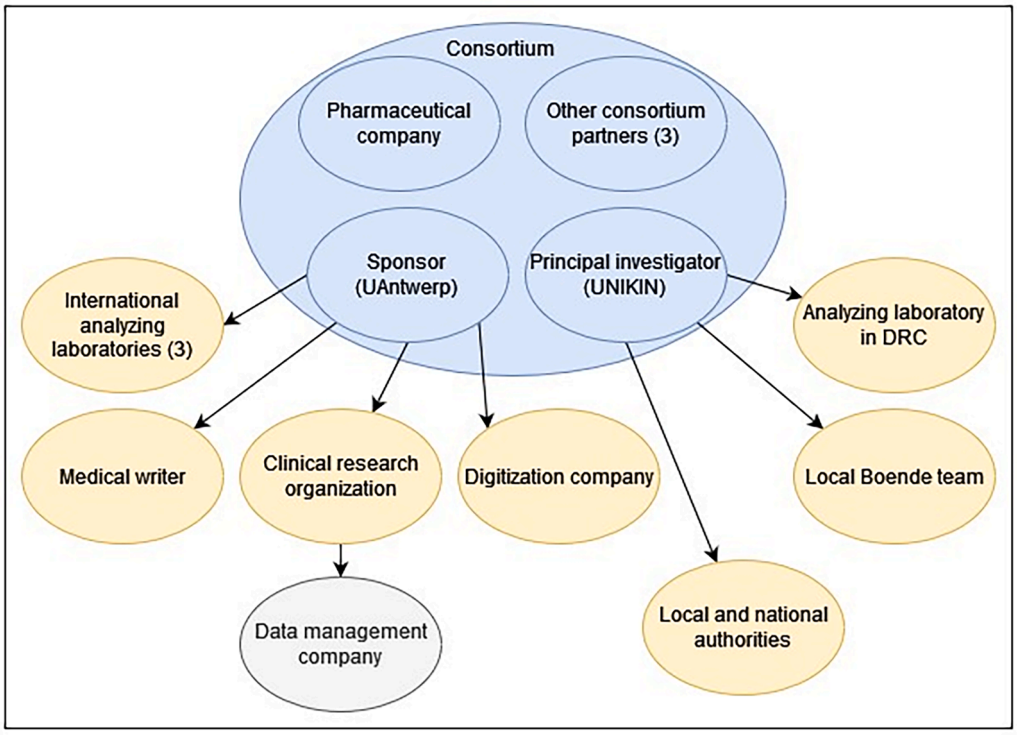

Fig. 3. International collaboration diagram of the EBL2007 trial based on contractual links This diagram shows the contractual links between different stakeholders. However, the communication between the different stakeholders was even more intertwined. For example, the sponsor team also had contact with the national analyzing laboratory (meetings), the local Boende team (training), and the data management company (meetings), while the Principal Investigator team also had contact with the clinical research organization (meetings and monitoring visits) and data management company (meetings).

agreements, it was paramount for sponsor administrators to provide close follow-up and capacity training, and to collaborate closely with the teams in the field in Boende and Kinshasa to develop an almost tailor-made, project-specific accounting system. Therefore, we recommend that all partners' administrative coordinators are involved from the start of the project, ideally already in the proposal phase, to develop an adapted project reporting that enables a smooth operational roll out in all involved countries.

The forementioned differences between the specific administrative set up, of the funder and its financial auditors and the local reality and practices of partners in LMICs, can increase the potential for misunderstandings and inaccurate conclusions. Practically, this risked stalling the project due to delays in funding and the entailing financial uncertainties. Therefore, anticipating auditors' requests, while documenting everything meticulously, is a way to avoid delays or even a possible (temporary) blocking of the funding in a project. Additionally, we recommend that consortium coordinators should assist less experienced partners in finding solutions to auditor's requests by combining the experience and know-how of their financial and administrative staff. The most experienced partners in the consortium should provide support to others for the benefit of the project as a whole.

When drafting project proposals and grant and consortium agreements, there is a tendency to focus on the research and operational field work, inadvertently paying less attention to the organizational and administrative aspects. Involving and consulting the administrative project coordinators already at the early stages is therefore strongly recommended.

Finally, operational, and logistical tasks in a cash-reliant environment (as is often true for LMICs) were made more difficult because three currencies were involved for the EBL2007 trial; the funders' Euro, the local currency (Congolese Franc) and the US dollar which often replaces the local currency. This set-up required a very close follow up of the cash movements for the different currencies by means of a well-structured cash ledger and close monitoring of the exchange rates. A continuous close cooperation with the financial administrators, and their empowerment, was paramount in controlling the substantial cash movements while at the same time complying with the funder's guidelines.

3. Conclusion

Overall, the EBL2007 trial was a great success. After more than 2.5 years of visits and follow-up, 92% of participants completed the study. We believe open, honest, and frequent communication among partners, with local authorities, trial staff and participants contributed greatly to this success. By assigning roles and responsibilities in the very beginning of the trial, all partners were aware of what was expected of each other. Frequent meetings (weekly or monthly) between partners ensured agreements were followed and adapted when necessary. In doing so, logistically the trial was well-organized and able to stay on track, even during unexpected events such as the COVID-19 pandemic. Additionally, we recommend other researchers to ensure participants and relevant authorities are informed of trial results through dissemination activities. This way, good relations can be maintained and future research opportunities in the area will have more likeliness of success. This paper was written in the same spirit of open communication and by sharing the challenges we encountered, how we mitigated them and the lessons that were learned, we hope to help other researchers aspiring to perform successful trials in similar settings of LMICs.

Funding

The EBOVAC3 project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 800176. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program, European Federation of Pharmaceutical Industries and Associations (EFPIA) and

the Coalition for Epidemic Preparedness Innovations (CEPI). All vaccines were provided by Janssen Vaccines & Prevention B.V.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

The authors gratefully acknowledge the hard work and dedication of the local trial staff. The supportive role of ACE Research (Clinical Research Organization), DFNet Research (Data management), and all partners within the EBOVAC3 Consortium is highly appreciated.

All authors attest they meet the ICMJE criteria for authorship.

References

[1] Lang T, Siribaddana S. Clinical trials have gone global: is this a good thing? PLoS Med 2012;9(6):e1001228.
[2] Larivière Y, et al. Open-label, randomised, clinical trial to evaluate the immunogenicity and safety of a prophylactic vaccination of healthcare providers by administration of a heterologous vaccine regimen against Ebola in the Democratic Republic of the Congo: the study protocol. BMJ Open 2021;11(9): e046835.
[3] Maganga GD, et al. Ebola virus disease in the Democratic Republic of Congo. N Engl J Med 2014;371(22):2083–91.
[4] Rosello A, et al. Ebola virus disease in the Democratic Republic of the Congo, 1976-201. Elife 2015; 4.
[5] Kilmarx PH, et al. Ebola virus disease in health care workers–Sierra Leone, 2014. MMWR Morb Mortal Wkly Rep 2014;63(49):1168–71.
[6] Doshi RH, et al. Risk factors for Ebola exposure in health care workers in Boende, Tshuapa Province, Democratic Republic of the Congo. J Infect Dis 2022;226(4): 608–15.
[7] Hayasaka E. Approaches vary for clinical trials in developing countries. JNCI: J Natl Cancer Instit 2005;97(19):1401–3.
[8] Martellet L, et al. Ethical Challenges and Lessons Learned During the Clinical Development of a Group A Meningococcal Conjugate Vaccine. Clin Infect Dis 2015; 61 Suppl(5(Suppl 5)):S422–7.
[9] Mbuagbaw L, et al. The challenges and opportunities of conducting a clinical trial in a low resource setting: the case of the Cameroon mobile phone SMS (CAMPS) trial, an investigator initiated trial. Trials 2011;12:145.
[10] Toto N, et al. Conducting clinical trials in sub-Saharan Africa: challenges and lessons learned from the Malawi Cryptosporidium study. Trials 2020;21(1):680.
[11] Zola Matuvanga T, et al. Setting-up an Ebola vaccine trial in a remote area of the Democratic Republic of the Congo: Challenges, mitigations, and lessons learned. Vaccine 2022;40(25):3470–80.
[12] RDC, M.d.l.S.d.l. Lignes directrices de l'évaluation éthique de la recherche impliquant des sujets humains en République Démocratique du Congo 2006 [cited 2023 16 June 2023]; Available from: https://clinregs.niaid.nih.gov/sites/default/files/documents/DRC/G-EthicalEval.pdf.
[13] Kass NE, et al. The structure and function of research ethics committees in Africa: a case study. PLoS Med 2007;4(1):e3.
[14] Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans 2016. Available from: https://cioms.ch/wp- content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf.
[15] Belsky L, Richardson HS. Medical researchers' ancillary clinical care responsibilities. BMJ 2004;328(7454):1494–6.
[16] Lemey G, et al. Algorithm for the support of non-related (serious) adverse events in an Ebola vaccine trial in the Democratic Republic of the Congo. BMJ Glob Health 2021;6(6).
[17] Lemey G, et al. Researchers' responsibilities in resource-constrained settings: experiences of implementing an ancillary care policy in a vaccine trial in the Democratic Republic of the Congo. Research Ethics 0(0): p. 17470161231194139.
[18] Innovative health Initiative. We are an EU public-private partnership funding health research and innovation. 13 February 2023]; Available from: https://www.ihi.europa.eu/.
[19] EUR-Lex. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance; 2022: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536.
[20] European Medicines Agency. Guideline for good clinical practice E6(R2). In: EMA/CHMP/ICH/135/1995, European Medicines Agency, Editor; 2016: https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline.
[21] Barnason S, et al. Emergency nursing resource: non-invasive temperature measurement in the emergency department. J Emerg Nurs 2012;38(6):523–30.
[22] World Health Organization. Interagency Emergency Health Kit 2017; 2017; Available from: https://www.who.int/emergencies/emergency-health-kits/interagency-emergency-health-kit-2017.
[23] World health Organization. Model List of Essential Medicines; 2021; Available from: file:///C:/Users/YLariviere/Downloads/WHO-MHP-HPS-EML-2021.02-eng-1.pdf.
[24] Zola Matuvanga T, et al. Use of Iris scanning for biometric recognition of healthy adults participating in an Ebola vaccine trial in the Democratic Republic of the Congo: Mixed Methods Study. J Med Internet Res 2021;23(8):e28573.
[25] Pushak N, Briceno-Garmendia C. The republic of Congo's infrastructure: a continental perspective. World Bank Policy Res Working Paper 2011:5838.
[26] Zola Matuvanga T, et al. Challenges to COVID-19 vaccine introduction in the Democratic Republic of the Congo - a commentary. Hum Vaccin Immunother 2022; 18(6):2127272.