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A feasibility study prior to an international multicentre paediatric study to assess pharmacokinetic/pharmacodynamic sampling and sample preparation procedures, logistics and bioanalysis

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ABSTRACT

Background: Variability in pre-analytical procedures such as blood sampling, sample preparation and transport can substantially influence bioanalytical results and subsequently impair reliability of data gathered during clinical trials. Especially in vulnerable populations, all efforts should be made to facilitate high-quality data extraction excluding unnecessary or repeated intervention.

Methods: The EU-funded LENA project (Labeling of Enalapril from Neonates up to Adolescents) included a feasibility study in its preparatory procedures prior to first-in-child studies. Derived from a regular study visit, it encompassed all procedures, from sampling of two study-specific drugs and four sensitive humoral parameters to bioanalysis, to evaluate the quality of obtained samples and applicability of logistical and bioanalytical procedures. Drug administration to healthy adults was circumvented by pre-spiking the blood collection tubes with a drug solution. Five clinical sites were evaluated.

Results: Clinical teams' preparedness and applicability of required sampling procedures was investigated in 18 volunteers, on-site. 97% of collected pharmacokinetic (PK) samples and 93% of samples for humoral parameters were obtained eligibly. Results met expectations, though one team had to be re-trained and performed a re-run. Planned procedures for sampling, sample preparation, transport and analysis were found to be suitable for being applied within paediatric trials.

Conclusion: The concept of the presented feasibility study that simultaneously assesses PK/PD sampling, sample preparation, logistics and bioanalysis proved to be a promising tool for trial preparation. It revealed improperly installed processes and bottlenecks that required adjustments prior to start of recruitment. It facilitated high-quality conduct from the first moment of paediatric pivotal studies.

1. Introduction

The quality of pre-analytical procedures such as blood sampling as well as sample preparation and transport can considerably affect the results of bioanalytical determinations. This has been reported for electrolytes [1], metabolomics [2,3], protein markers [4] and drugs [5–7]. Especially in clinical trials, study outcomes might be biased without adequately controlled quality of the pre-analytical procedures [2,8], which cannot be compensated by highly sophisticated and validated methods of determination [2]. Thus, pre-analytical procedures ought to be standardised in advance, especially for trials in vulnerable populations, to prevent unnecessary or repeated interventions. This is typically done only through a short training of staff during the site initiation visit for a clinical trial.

Between 19% and 40% of randomised controlled paediatric trials were found to have been discontinued [9,10]. Amongst the main reasons for discontinuation were conduct problems including logistical and technical issues. Investigators have made some attempts to avoid trial failure due to non-adherence to protocol or incomplete data sets [11]. Small-scale studies such as pilot or feasibility studies prior to a main study are performed to verify the site performance and enhance trial success [12,13]. Some researchers even claimed that it seems unethical

Abbreviations: ACE, Angiotensin-converting-enzyme; Cmax, maximum serum concentration; ELISA, Enzyme-linked immunosorbent assay; EMA, European Medicines Agency; EU, European Union; FDA, U.S. Food and Drug Administration; GCP, Good Clinical Practice; LC-MS/MS, Liquid chromatography-tandem mass spectrometry; LENA, Labeling of Enalapril from Neonates up to Adolescents; PD, Pharmacodynamic(s); PK, Pharmacokinetic(s); pp, Percentage points; RAA system, Renin-angiotensin-aldosterone system; RIA, Radioimmunoassay

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to conduct a study whose feasibility has not been verified [12]. Most of these feasibility or pilot studies focus on aspects of processes, resources, management and/or science of the main study [12]. For example, they may assess the randomisation procedure, recruitment rate or suitability of assessment procedures and outcome measures [11,13]. Ideally, they should target identified risk factors for successful completion of the main trial [14].

Especially prior to paediatric trials, pilot or feasibility studies should be performed to verify applicability of procedures and performance of clinical sites, to avoid unnecessary clinical investigations in the highly vulnerable paediatric population [15]. Therefore, investigators of the LENA trials ('Labeling of Enalapril from Neonates up to Adolescents') trials performed a feasibility study. They identified the most challenging aspects of trial conduct. These were the highly sophisticated blood-sample preparation procedures for pharmacokinetic (PK) and several pharmacodynamic (PD) parameters, aimed at avoiding incorrect determination of temperature-sensitive substances with short half-lives that subsequently causes non-reliable data.

2. Materials and methods

2.1. The LENA project

The LENA project is an international academic research project funded by the European Commission. It aims to investigate orodispersible enalapril minitablets administered to children suffering from heart failure. Alongside pharmacokinetics (PK), several sensitive humoral parameters for evaluation of pharmacodynamics (PD) are determined, aiming to improve the understanding of the maturating renin-angiotensin-aldosterone system (RAA system) and its response to drug therapy with angiotensin-converting-enzyme (ACE) inhibitors. The demanding sampling and sample preparation procedures have already been subject to joint, comprehensive training for involved clinical teams, prior to the presented feasibility study.

2.2. Feasibility study within the LENA project

The intended pivotal paediatric studies of the LENA project aim to obtain reliable pharmacokinetic data of the ACE inhibitor enalapril and its active metabolite enalaprilat (primary study endpoint) as well as to consistently determine alterations in humoral parameters (secondary study endpoint). To ensure that right from the beginning of the pivotal studies high quality PK and PD data is generated, the objective of the here presented feasibility study, was to investigate the clinical teams' ability to perform the challenging sampling-related procedures and obtain samples within the pre-defined specifications. It assessed feasibility of planned procedures related to collection, transport and bioanalysis of PK/PD samples.

2.3. Ethical approvals

Clinical sites obtained ethical approval (or confirmation that an approval for this specific kind of study was not required) before participating in the feasibility study (EK 1690/2015 at the Medical University of Vienna, WT/aj/247957 at the Erasmus Medical Center in Rotterdam, WAG/mb/15/037193 at the University Medical Center Utrecht, and REC no. 16/SC/0124 at the Great Ormond Street Hospital). In addition, the University Clinics' ethics committee in Dusseldorf, where the project's central laboratory is located, agreed on the protocol (Protocol No. 5118). The work has been carried out in accordance with the Declaration of Helsinki. The data protection concept/privacy rights of the investigation complied with the regulations of North Rhine-Westphalia (Germany) being regarded as one of the strictest in Europe.

2.4. Inclusion/exclusion criteria for participation in the feasibility study

Healthy adults without cardiovascular diseases and without any current medication (self-reported), aged between 18 and 50 years, were eligible for participation. Volunteers whose (self-reported) health condition raised medical concerns against blood withdrawal (e.g., anaemia) were excluded. All participants provided informed consent prior to the start of the study.

2.5. Study design and conduct

The feasibility study was designed to mimic the study sampling procedures of a regular LENA study visit within the paediatric studies. Details on performed procedures are provided in Fig. 1. The exact date of conduct was chosen individually for each clinical site, according to the anticipated start of recruitment. Areas assessed at the clinical sites included sampling, on-site sample preparation, documentation and dispatch of samples to the central laboratory of the LENA project for subsequent analysis as well as evaluation of results. Each clinical site performed corresponding procedures on three adult volunteers. Staff members were encouraged to rotate tasks, e.g., blood collection, documentation, and sample preparation. This ensured that every member of staff ran through all procedures that would come up during the trials. In this feasibility study, clinical teams of five clinical sites from four countries (Great Britain, The Netherlands, Austria, and Hungary) were involved.

Sampling requirements encompassed blood withdrawal for the compounds of interest in the paediatric trials of the LENA project. For the PK-related primary outcomes, the compounds are enalapril and its metabolite enalaprilat. The humoral parameters aldosterone, renin, plasma renin activity and angiotensin I are of interest as secondary outcome measures for exploratory PD investigations [16–18]. All samples were collected and labelled in accordance with the approved pseudonymisation process. Due to the sensitivity and poor stability of investigated peptides and hormones, all samples required immediate on-site sample preparation. Procedural instructions were applied as outlined in the corresponding LENA manual on sampling and sample preparation. This included a fixed sampling and sample preparation sequence, a strict time limit and specific temperature conditions to be applied during sampling, clotting time as well as centrifugation, depending on the type of the sample matrix. Blood samples for temperature sensitive humoral parameters were drawn with the blood collection tube enveloped in an ice pack and transported on ice to further preparation. All samples were centrifuged for 10 min at 2000 × *g*, at either room temperature or 4 °C depending on temperature sensitivity. The supernatant was subsequently transferred to cryo-tubes and snap frozen in a methanol/dry ice bath. Depending on the sensitivity of the substance of interest, applicable time limits to proceed from sampling to snap freezing of the supernatant were defined as 15 or 30 min. The consumables used and all on-site laboratory equipment utilised were identical to equipment intended for the paediatric trials, including the small-scale sampling material for paediatric use, the layout for labels and all form sheets required.

2.6. By-pass of drug administration

Bearing in mind ethical constraints on unnecessary drug administration to healthy volunteers, a special concept to by-pass drug application was developed to avoid administration of a drug during the feasibility study. This avoidance was achieved by pre-spiking the blood collection tubes with a stock solution of the drugs. The spiking took place in batches at the Institute of Clinical Pharmacy and Pharmacotherapy (Dusseldorf, Germany). The spiking procedure is illustrated in Fig. 2. The volume and concentration of the spiked drug solution is based on calculations regarding the final concentrations per blood-filled tube without substantial dilution of blood collected.