## 8 THE INFLUENCE OF SEPSIS ON THE TISSUE PENETRATION OF PIPERACILLIN-TAZOBACTAM IN CHILDREN: A MICRODIALYSIS STUDY IN THE JUVENILE PIG

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**Introduction** Antibiotics are the cornerstone in the treatment of sepsis. Microdialysis (MD) data from adults suggest an impaired antibiotic tissue penetration in the case of sepsis. Tissue pharmacokinetics (PK) remain largely understudied in children. Juvenile pig models have proven to provide an accurate prediction of PK behavior in pediatric patients. This study aimed to investigate the influence of sepsis on antibiotic tissue penetration in a piglet model.

**Methods** In 17 piglets, piperacillin (PIP) - tazobactam (TAZ) was administered (75 mg/kg IV over 30 minutes, 6h dosing interval) over 4 days. Blood and MD samples (muscle) were collected in first-dose (FD) and steady-state (SS) conditions. In 11 piglets a continuous LPS infusion (36h) was administered to induce a septic state. In the 6 control animals (no LPS) time effects during the study period were evaluated. Non-compartmental PK analysis was used to determine the tissue penetration (AUC-ratio tissue/plasma). The AUC ratios were pairwise compared between the healthy and septic states in each piglet, data are reported as mean ± SD.

**Results** For PIP, the AUC ratio in FD conditions was significantly lower in the septic state (0.84 ± 0.22) compared to the healthy baseline measurement (1.06 ± 0.46) (P = 0.042). In SS conditions, comparable results were found with an AUC ratio of 1.09 ± 0.27 during baseline and 0.80 ± 0.22 in the septic state (p=0.009). The results for TAZ were similar to PIP. There were no time effects found in the control group.

**Conclusion** In this juvenile piglet model, sepsis impaired the PIP-TAZ tissue penetration. The results of this study warrant further research into the tissue PK of septic children to optimize the antibiotic dosing in this population.

## 9 THE FLOOD OF STUDY FEASIBILITIES AND THE VALUE OF A CENTRALISED APPROACH

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**Introduction** Due to an increase in multicentric paediatric clinical trials after 2007 following the EU Paediatric Regulation, there has been a substantial increase in the number of feasibility questionnaires (FQ). Paediatric clinical trial conduct has made unique advances through the conect4children (c4c) pan-European network, funded by the Innovative Medicines Initiative (IMI2). We examined the role of a national, centralized coordination center in Belgium to pre-fill feasibility questionnaires and quality control responses from sites.

**Methods** This report describes the 4-year learnings of prefilling and performing quality control for FQ by the Belgian Network representative. Additional information has been included from a broad survey sent to sites in the Belgian Network, of which 13 of the 15 sites have responded.

**Results** PIs are confronted by between 10 to 50 FQ requests per year, each taking at average 60 minutes. The number of redundant questions asked by sponsors is on average 43% of the FQ. Of the 112 completed feasibilities, approximately 82% required quality control adjustments by our national coordinating center. Inconsistencies were primarily found in PIs' report of experience, number of paediatric studies conducted, recruitment estimates and site qualifications. With a centralized and repetitive collection of FQ, a prefill of 65% of the requested information and potential corrections can be performed. A time reduction of 10 to 46% is estimated when a FQ is facilitated through the national representative.

**Conclusions** The increase in paediatric clinical trials has substantially burdened sites within Belgium. Quality control and adjustments by a national central organization could be beneficial to increase feasibility quality and efficiency.

## 10 PAEDIATRIC CLINICAL TRIAL NEEDS AND REQUIREMENTS WITHIN BELGIUM

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**Introduction** Due to the Paediatric Regulation in 2007, the number of paediatric clinical trials within Europe has substantially increased. Consequently, potential sites for paediatric clinical trials were overrun by trial opportunities, infrastructure pressure and their limited experience. To support sites and facilitate research, the pan-European network conect4children (c4c) was established and funded by the Innovative Medicines Initiative (IMI2). In order to attain sustainable research networks, site requirements innovation needs require further investigation.

**Methods** A questionnaire was conducted within the c4c Belgian Clinical trial network. An inquiry was made into the role of a national hub and other topics for support. Due to multiple responses per site, answers were grouped per site.

**Results** Of the 15 connected sites, we received 32 responses coming from 13 unique sites. Within the Belgian network, around 4 (30%) of sites do not have a paediatric clinical trial unit to support trials. All sites agreed or strongly agreed that a national hub is useful for the site to conduct clinical trials. The majority namely 11 (84%) of sites identified human resources as a core improvement need for sites, specifically finding dedicated clinical research nurses and finding time for principal investigators (PI) to perform study tasks aside from clinical work. A strong need for financing of infrastructure from 10 (76%) of sites is acknowledged for consultation areas, imaging, and a biobank structure.

**Conclusions** In order to foster sustainable development of new medicines in paediatric diseases, site need's must to be taken into account and prioritized. The primary need is in human resources and financing of infrastructure.