



Eveleens, R.D., Gerasimidis, K., Chourdakis, M., Huysentruyt, K., Koletzko, B., Hulst, J.M. and Joosten, K.F.M. (2018) Current clinical trials in paediatrics: report of the ESPEN special interest group in paediatrics. *Clinical Nutrition ESPEN*, 27, pp. 75-78. (doi:[10.1016/j.clnesp.2018.06.006](https://doi.org/10.1016/j.clnesp.2018.06.006)).

This is the author's final accepted version.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/164321/>

Deposited on: 21 June 2018

Enlighten – Research publications by members of the University of Glasgow  
<http://eprints.gla.ac.uk>

## **Current Clinical Trials in paediatrics: report of the ESPEN Special Interest Group in**

### **Paediatrics**

Eveleens RD<sup>a</sup>, Gerasimidis K<sup>b</sup>, Chourdakis M<sup>c</sup>, Huysentruyt K<sup>d</sup>, Koletzko B<sup>e</sup>, Hulst JM<sup>f</sup>, Joosten KFM<sup>a,\*</sup>

*<sup>a</sup> Department of Pediatrics and Pediatric Surgery, Intensive Care Unit, Erasmus Medical Centre - Sophia Children's Hospital, Rotterdam, The Netherlands; <sup>b</sup> Human Nutrition, School of Medicine, College of Medicine, Veterinary and Life Sciences, Royal Hospital for Sick Children, University of Glasgow, Glasgow, United Kingdom; <sup>c</sup> Medical School, Faculty of Health Sciences, Aristotle University of Thessaloniki, University Campus, Greece; <sup>d</sup> Department of Paediatric Gastroenterology, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium; <sup>e</sup> LMU -Ludwig-Maximilians-University of Munich, Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children's Hospital, University of Munich Medical Centre, Munich, Germany; <sup>f</sup> Department of Pediatrics, Division of Pediatric Gastroenterology, Erasmus Medical Centre - Sophia Children's Hospital, Rotterdam, The Netherlands*

**\* Corresponding author:** Koen FM Joosten, Erasmus MC-Sophia Children's Hospital, Department of Paediatrics, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands, Phone: +31107040704, E-mail: k.joosten@erasmusmc.nl

**MANUSCRIPT WORD COUNT:** Abstract: 209; Full text: 1972 words;

3 Figures; 1 Table

**Keywords:** Paediatrics, special interest group, clinical trials, nutrition

2 **Abstract**

3 **Background & Aims:** At the 38<sup>th</sup> annual ESPEN congress in The Hague, the Netherlands, the  
4 Special Interest Group (SIG) in Paediatrics presented data about current research activities in  
5 the field of paediatric nutrition which are performed worldwide and translated this to future  
6 research perspectives.

7 **Methods:** Extensive search of all registered observational and interventional clinical trials in  
8 the database ClinicalTrials.gov using the search terms: children nutrition, paediatrics  
9 nutrition and children feeding.

10 **Results:** A total of 717 studies were found; 173 were duplicates and 114 included adult  
11 participants and were therefore excluded. Hence, 430 remained for analysis, of which 69%  
12 were randomized controlled trials. The most investigated research topic was nutrition in  
13 specific diseases (n=98), followed by obesity (n=92), and studies including premature infants  
14 (n=48). The overall median estimated enrolment of children in the trials was 150 children  
15 [IQR 50 - 365]. There were 44 studies in which >1,000 participants will be enrolled and six  
16 studies with >10,000 participants. Studies including >1,000 participants were primarily  
17 performed in North America (39%), Africa (27%), and Europe (16%).

18 **Conclusions:** This SIG report showed that 430 clinical nutrition trials in paediatrics are  
19 registered and current research focusses primarily on specific diseases and obesity. The SIG  
20 paediatrics encourages future research to invest in well-controlled interventional trials.

21 **1. Introduction**

22 In September 2017 at the 38<sup>th</sup> European Society for Clinical Nutrition and Metabolism  
23 (ESPEN) congress in The Hague, the Netherlands the ESPEN special interest group (SIG) in  
24 Paediatrics had its annual meeting. One of the objectives of SIG Paediatrics is to coordinate,  
25 promote, or develop research projects or programs of studies in clinical nutrition in  
26 hospitalized and outpatient children and to develop position statements (1). The aim of the  
27 current manuscript is to report about ongoing paediatric research activities worldwide,  
28 which are registered in ClinicalTrials.gov and discuss future research activities that might be  
29 useful.

30

31 **2. Methods**

32 To gain an overview of all the current trials performed in the field of clinical nutrition in  
33 paediatrics the website ClinicalTrials.gov was used. The website provides the ability to find  
34 individual trials, but also search for them using certain terms. The following three search  
35 terms were entered in the search field: “Children AND Nutrition”, “Paediatrics AND  
36 Nutrition”, and “Children AND Feeding”. Trials were included in this search if: 1) Participants  
37 were children in the age range 0-18 year; 2) Design of the trial was intervention and/or  
38 observational 3) Status of trial was recruitment or pre-recruitment. No limits were selected  
39 with regard to gender, study results, study phase and funder type. Data acquisition was  
40 completed on 8<sup>th</sup> of August 2017 prior to the ESPEN annual meeting.

41 Data collected for subsequent analysis were the start and (expected) completion date  
42 of primary outcome, title, study type, study design, estimated enrolment number, gender,  
43 minimum and maximum age, sponsor, country where research is performed and number of

44 centers included. The investigators of the registered trials need to select the condition,  
45 usually the main topic or disease, in which their research is performed. For example, an  
46 investigator was interested in undernutrition within Crohn's disease. When registering the  
47 trial the investigator need to select a condition (topic or disease field), which can either be  
48 undernutrition or Crohn's disease in this example. Therefore, conditions from  
49 ClinicalTrials.gov were based on what the investigators of the trials found the most  
50 important and suitable condition for their research. We collected the conditions of the  
51 investigators and used them to classify the main topic of the trials in our database, which  
52 was performed by one observer (RE). The trial characteristics were summarized and  
53 reported as counts and percentages.

54

### 55 **3. Results**

56 With applying the three search terms, 717 studies were found, out of which 173 were  
57 duplicates and 114 included adult populations and were therefore excluded (**Fig. 1**). Hence,  
58 430 studies were brought forward for further analysis. Sixty-nine percent of the studies were  
59 randomized controlled trials (RCT), 18% non-randomized intervention trials and 13%  
60 observational studies. Most of the studies were performed in North America (49%), Europe  
61 (24%) and Asia (17%) (**Table 1**); 53% of the studies were single center research. The studied  
62 population consisted only of infants in 25% and only adolescents in 2% of the studies. The  
63 expected date of study completion was for 213 studies in 2017 and 10 in 2018.

64 Fifteen different research topics were identified within paediatric nutrition research.  
65 The most investigated research topic was nutrition in specific diseases (n=98), followed by  
66 obesity (n=92), and studies including premature infants (n=48) (**Fig. 2**). Obesity and

67    undernutrition combined accounted for 27% (n=116) of all research. Studies related to  
68    obesity were predominantly performed in North-America (67%) and Europe (23%), whereas  
69    studies regarding undernutrition in the general population were performed in Africa (50%)  
70    and Asia (28%). Hospital undernutrition was mostly investigated in Asia (68%) and  
71    undernutrition resulting from anorexia nervosa in Europe (100%). Trials investigating obesity  
72    were mostly based on educational, nutritional or exercise intervention (n=80). (Epi)genetics,  
73    altered pharmacokinetics and development were also investigated.

74            A total of 98 studies investigated nutrition within specific diseases, of which 30 were  
75    performed in gastrointestinal diseases, such as Crohn's disease (n=10), inflammatory bowel  
76    disease (n=5), and short bowel syndrome (n=2). Other investigated areas were children with  
77    respiratory diseases (n=11) and neurological conditions (n=10) (**Fig. 3**). The median  
78    estimated number of participant enrolment was 150 children [IQR 50 - 365]. There were 44  
79    studies in which  $\geq 1,000$  participants will be enrolled and six studies with  $>10,000$   
80    participants. Studies including  $\geq 1,000$  participants were primarily performed in North  
81    America (39%), Africa (27%), and Europe (16%). The three largest nutrition RCT were: 1) a  
82    double-blind RCT on antibiotics for children with severe diarrhoea in Kenya; 2) a RCT  
83    investigating the impact of promoting community initiated kangaroo mother care for low  
84    birth weight Infants in India; 3) a single arm RCT investigating a nutritional care program and  
85    psychosocial stimulation to improve malnourished children's development in Bangladesh.

86

#### 87    **4. Discussion**

88    This analysis of the currently ongoing clinical trials worldwide showed that most reported  
89    studies were randomized clinical trials, in single centers and performed predominantly in

90 North America. The major research topics registered were obesity and disease specific  
91 nutrition. Interestingly within the topic obesity, most studies concerned behavioural  
92 nutritional interventions and within the topic disease specific most studies were related to  
93 gastrointestinal diseases.

94 Last year the ESPEN Paediatric SIG reported that it was an important priority to test  
95 hypotheses generated from association studies within well-controlled trials and explore the  
96 effectiveness of nutritional interventions in improving patients' clinical outcomes and  
97 disease prognosis (1). Therefore, we were within this study primarily interested in well-  
98 designed and adequately powered RCT's. Unfortunately, information on power calculations  
99 were not presented on ClinicalTrials.gov. Nevertheless, to present an overview of relevant  
100 RCT's which are likely to influence future guidelines we decided to display large trials with an  
101 arbitrary cut-off value of 1,000 participants. First, it was remarkable that large RCT's were  
102 relatively more performed in low and medium income countries. The three largest trials  
103 were performed in Kenya, India and Bangladesh. Secondly, we could identify only a limited  
104 number of large RCT's which might have an impact on the development of clinical guidelines  
105 and three upcoming trials should be highlighted. First, the long-term follow up of the  
106 PEPaNIC study investigating the effect of supplemental parenteral nutrition on long-term  
107 neurocognitive outcome in critically ill children. Second, a RCT on the induction of early  
108 solids foods on the food tolerance in babies, and third, a nurse-led parent educational  
109 support intervention for discharged children with newly diagnosed cancer.

110 The impact of the results of these ongoing studies in children is yet unknown.  
111 Recently, the European Society for Paediatric Gastroenterology Hepatology and Nutrition  
112 (ESPGHAN), the European Society of Paediatric Research (ESPR) and ESPEN have jointly  
113 developed new guidelines for paediatric PN (2), while ESPGHAN and the European Society of

114 Paediatric and Neonatal Intensive Care (ESPNIC) are developing joint guidelines for nutrition  
115 in paediatric intensive care. In both guideline development processes it became obvious that  
116 there is a lack of high quality controlled nutritional interventional studies on important  
117 unresolved questions. An example of a published interventional study which will have an  
118 impact on the new guidelines is the multicenter PEPaNIC trial (3). This study showed that  
119 initiating parenteral nutrition (PN) after one week of critical illness as compared to starting  
120 on the first day of paediatric intensive care reduced newly acquired infections and  
121 accelerated recovery, with a shorter duration of mechanical ventilation and stay on the  
122 paediatric intensive care and in the hospital. However, there was a significant increased risk  
123 of developing hypoglycemia and therefore follow-up research is needed before definitive  
124 recommendations can be made (4, 5). New guidelines will take the results of the PEPaNIC  
125 study into account. Additional research is needed to more accurately determine the dosing  
126 and timing of administration of PN in critical illness. Another future research of interest in  
127 critically ill children is the amount of EN in relation with periods of fasting and the circadian  
128 rhythm.

129         There is an unmet need for more studies exploring the role of nutritional  
130 interventions and how this can improve, not only nutritional, but also clinical outcomes in  
131 healthy children and in patients with different disorders. While there is substantial evidence  
132 exploring nutritional support in adult (mainly geriatric) patients (6-8), there appears to be a  
133 staggering lack of evidence from paediatric studies. Such interventions can span from  
134 diagnostic evaluation to therapeutic interventions such as dietary counselling, food  
135 fortification, supplementation with oral nutritional supplements and enteral and parenteral  
136 nutritional support. In these studies the effects of energy providing nutrients and  
137 micronutrients can be studied together or separately. The hypotheses tested in clinical trials

138 should ideally be backed up by data from preclinical and mechanistic studies, which are  
139 currently also frequently lacking.

140         There are some limitations of our survey. In this analysis we only used the  
141 ClinicalTrials.gov database. This database is run by the United States National Library of  
142 Medicine and was the first online registry for clinical trials and is the largest and most widely  
143 used today. There are other databases which can be screened as well, such as EU register,  
144 JPRN, ISRCTN, ANZCTR, but we did not incorporate these databases (9). We included  
145 observational and interventional trials, but only 13% of the registered trials were  
146 observational trials. Registration of interventional trials has become a prerequisite for  
147 publication in leading peer-reviewed journal, which possible resulted to a bias in our  
148 database.

149         In conclusion, in this SIG report it was shown that 430 clinical nutritional trials in  
150 paediatrics are currently registered with predominant focus on obesity and gastrointestinal  
151 diseases. There is need for more high quality, controlled intervention trials in paediatric  
152 nutrition.

154 **Statement of authorship**

155 RE and KJ collected and analysed the data. RE, KJ and KG drafted the first manuscript. All  
156 authors contributed to the data interpretation and revised the manuscript. All authors  
157 approved the final manuscript.

158

159 **Conflicts of interest statement and funding sources**

160 RE received a grant from Nutricia Research B.V., Utrecht, The Netherlands. Nutricia Research  
161 B.V. was not involved in the collection, analysis or interpretation of the data, nor were they  
162 involved in the decision to publish the results.

163

164 **Acknowledgements**

165 The authors thank Janneke de Wijs and Lisa Chadwick for their contribution to the data  
166 collection.

167

168 **Abbreviations**

169 ESPEN: European Society for Clinical Nutrition and Metabolism; ESPGHAN: European Society  
170 for Paediatric Gastroenterology Hepatology and Nutrition; ESPNIC: European Society of  
171 Paediatric Neonatal Intensive Care; ESPR: European Society of Paediatric Research; PN:  
172 parenteral nutrition; RCT: randomized controlled trials; SIG: Special interest group

173

174 **References**

175 1. Gerasimidis K, Hulst JM, Chourdakis M, Huysentruyt K, Koletzko B, Joosten KFM. The  
176 launch of the ESPEN Special Interest Group in Paediatric Clinical Nutrition. Clinical Nutrition

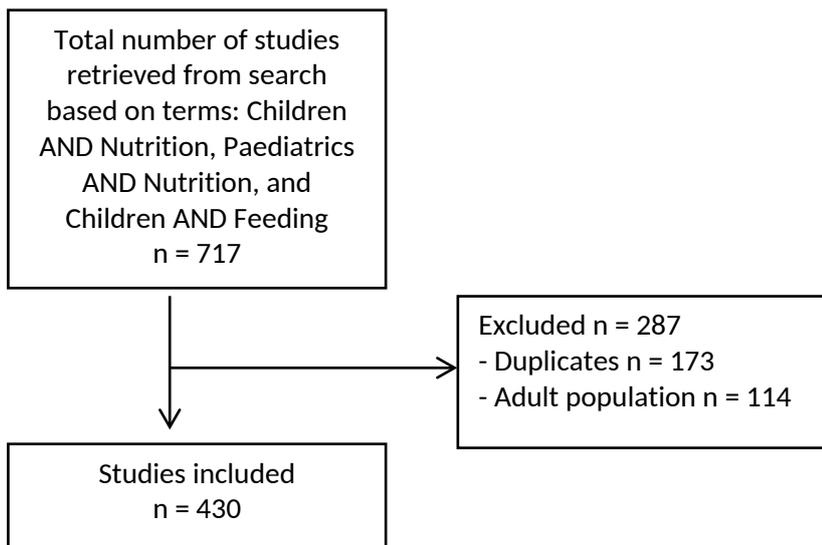
- 177 ESPEN. 2017;19((Gerasimidis K.) Human Nutrition, School of Medicine, College of Medicine,  
178 Veterinary and Life Sciences, Royal Hospital for Sick Children, University of Glasgow,  
179 Glasgow, United Kingdom):45-8.
- 180 2. ESPGHAN/ESPEN/ESPR/CSPEN Guidelines on pediatric parenteral nutrition. Clinical  
181 Nutrition. 2018.
- 182 3. Fizez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al.  
183 Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med.  
184 2016;374(12):1111-22.
- 185 4. Vanhorebeek I, Verbruggen S, Casaer MP, Gunst J, Wouters PJ, Hanot J, et al. Effect of  
186 early supplemental parenteral nutrition in the paediatric ICU: a preplanned observational  
187 study of post-randomisation treatments in the PEPaNIC trial. Lancet Respir Med.  
188 2017;5(6):475-83.
- 189 5. van Puffelen E, Vanhorebeek I, Joosten KFM, Wouters PJ, Van den Berghe G,  
190 Verbruggen SCAT. Early versus late parenteral nutrition in critically ill, term neonates: a  
191 preplanned secondary subgroup analysis of the PEPaNIC multicentre, randomised controlled  
192 trial. The Lancet Child and Adolescent Health. 2018; 2(7):505-515
- 193 6. Sobotka L, Schneider SM, Berner YN, Cederholm T, Krznaric Z, Shenkin A, et al. ESPEN  
194 Guidelines on Parenteral Nutrition: Geriatrics. Clin Nutr. 2009;28(4):461-6.
- 195 7. Volkert D, Berner YN, Berry E, Cederholm T, Coti Bertrand P, Milne A, et al. ESPEN  
196 Guidelines on Enteral Nutrition: Geriatrics. Clin Nutr. 2006;25(2):330-60.
- 197 8. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al. ESPEN  
198 Guidelines on Enteral Nutrition: Intensive care. Clin Nutr. 2006;25(2):210-23.

199 9. Huser V, Cimino JJ. Evaluating adherence to the International Committee of Medical  
200 Journal Editors' policy of mandatory, timely clinical trial registration. J Am Med Inform Assoc.  
201 2013;20(e1):e169-74.

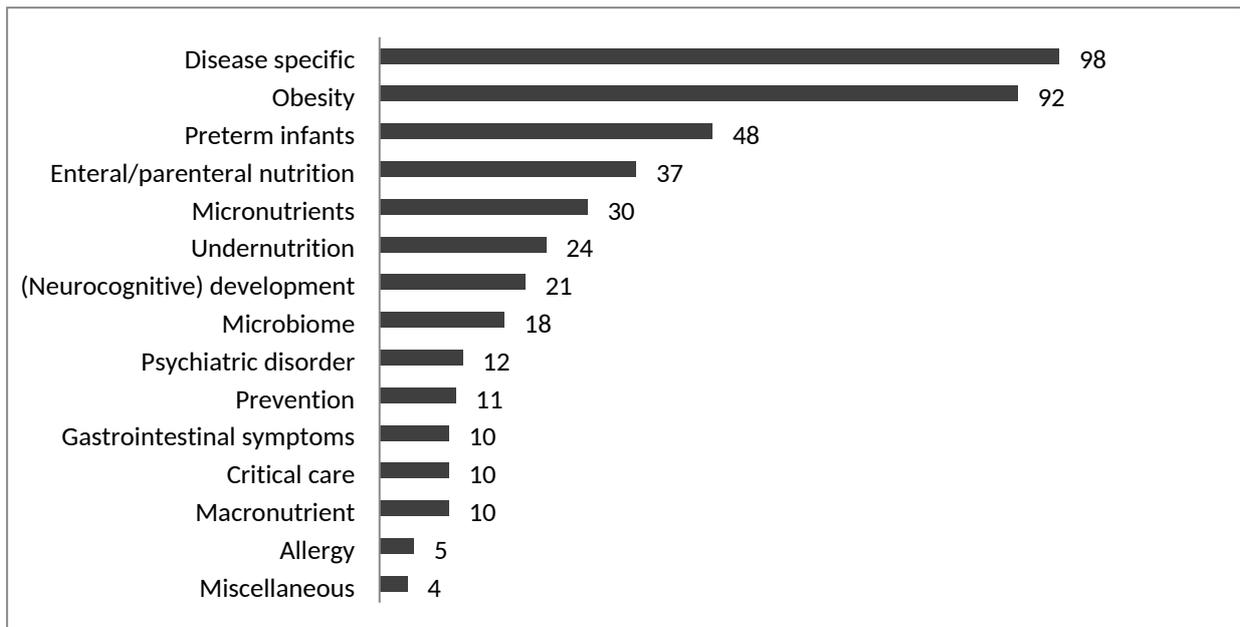
202 **Table 1.** Geographic location of performed research within paediatric clinical nutrition.

<b>Continents</b>		<b>Top 6 Countries</b>	
North-America	49%	United States	40%
Europe	24%	Canada	8%
Asia	17%	France	5%
Africa	7%	Israel	4%
South-America	2%	China	4%
Australia	1%	Bangladesh	3%

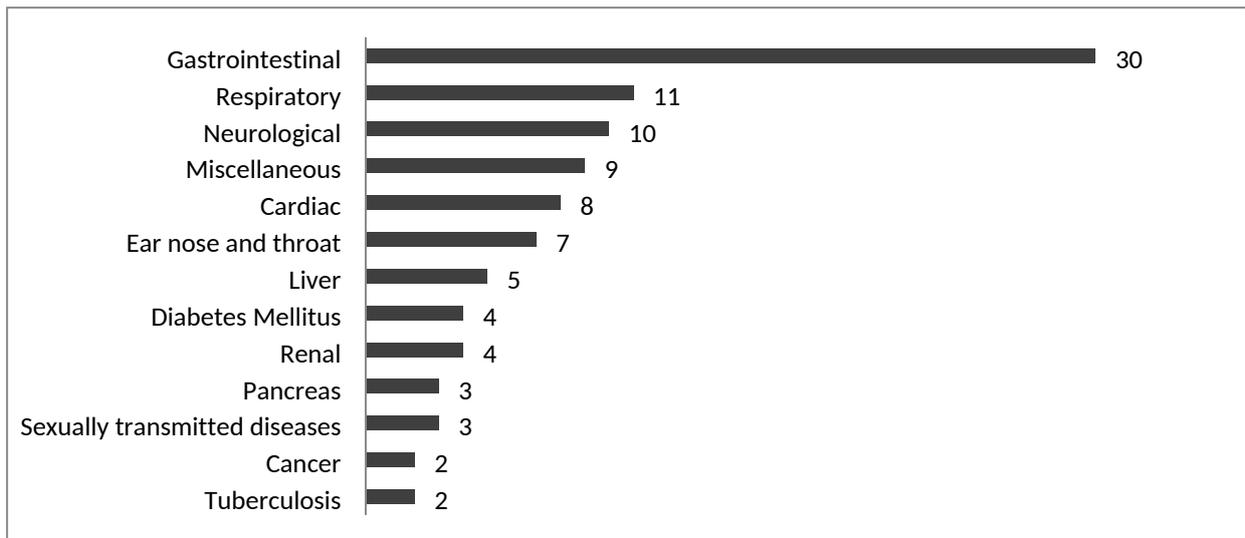
203



**Fig. 1.** Flowchart of search for clinical nutrition studies in children using database of ClinicalTrials.gov.



**Fig. 2.** Number of studies according to topics within paediatric clinical nutrition research (retrieved from ClinicalTrials.gov up to August 8<sup>th</sup> 2017)



**Fig. 3.** Disease specific topics within paediatric clinical nutrition research (total number = 98; retrieved from ClinicalTrials.gov up to August 8<sup>th</sup> 2017)