PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	**Pharmacokinetic research in children: an analysis of registered records of clinical trials**
AUTHORS	Viergever, Roderik; Rademaker, Carin; Ghersi, Davina

The above paper was submitted to the Archives of Disease in Childhood (ADC) but declined for publication following peer review. The authors addressed the reviewer's comments and submitted the revised paper to BMJ Open. The paper was subsequently reviewed by a BMJ Open reviewer with access to the ADC reviews.

ORIGINAL SUBMISSION – ADC REVIEW

REVIEWER	***Maurizio Bonati*** Mario Negri Research Institute Laboratory for Mother and Child Health Milano Italy

GENERAL COMMENTS	The reported work is original and probably unique. It may be of interest for ADC redears, but it should be improved as it can be also useful. Concerning the considered period: 22 May 2009 is too distant an up-date is necessary. A rate of PK-PD studies between adults and children should be interesting, also a discussion of different studied drugs vs age. Fig. 1 and 3 can be cancelled without affecting the information. A few details about drugs and clinical conditions taken into account in retrived trials should be reported and discussed. A comparison with the EMA list of priorities should be useful. The PK-PD laking data is only a small part of the off-label scenario, even if authors underline often this association. From the clinical point of view it should be interesting to know what these trials have produced or will produce for a better use of medicines in children in considered therapeutic conditions.

REVIEWER	***Dr Helen Sammons***

	Associate Professor of Child Health University of Nottingham

GENERAL COMMENTS	Thank you for asking me to review this interesting paper. There are still few clinical trials of pharmacokinetics (PK) performed in children and this paper helps highlight this. It provides a clear review of the current situation of PK within research currently taking place.The methodology was clear and the data extraction robust. It gives new original data on the current research situation. The conclusions on the topic and what the paper adds was sound and adds to the literature.My further comments for publication are below: Major points: 1) A brief summary of the registers making up the ICTRP would be helpful and summary of the regions in the world they cover. This would allow the reader to put data presented later into perspective on where the clinical trials took place. 2) There were 1075 trials investigating a medicine, of which 245 collected PK data. The paper then breaks these down into regions of the world. It would have been helpful to not only see the percentage of total PK studies taking place in each region (table 1) but to be able to quantify this by the number of trials taking place in each region. So, for example, there were 15 PK trials in north africa which were 6% of the total PK trials. Were these all the trials in north africa or only a small percentage? This then needs to be quantified in the discussion. Is there just more research in N America, but is PK still neglected in the same proportion of studies? This needs quantifying in the article and abstract. 3) Did they review any of the trials not collecting PK data to see if it would have been relevant to do so? 4)Pharmacodynamic data in only 1/5 of PK studies was mentioned- this needs to be discussed along with the phase of the study as 27% were phase one and others did not specify. Minor points: 1) i found Figure 2 difficult to read and i don't think it would

	reproduce easily in the journal. 2) The data only contained trials registered on the ICTRP, not the whole world. How inclusive is it?

ADC VERSION – AUTHOR RESPONSE

We have replied to the peer-reviewers' comments below in *italic*.

Reviewer 1 (Maurizio Bonati) Comments for the Author...

The reported work is original and probably unique. It may be of interest for ADC readers, but it should be improved as it can be also useful. Concerning the considered period: 22 May 2009 is too distant an update is necessary.

We agree that it would be very interesting to update this study with a dataset from a more recent date. We even address this point in our discussion (" … it is of great importance that the collection of pharmacokinetic data in clinical trials in children continues to be monitored in the future.") It is however not feasible for us to conduct this update for the purpose of this publication.

A rate of PK-PD studies between adults and children should be interesting, also a discussion of different studied drugs vs age.

Indeed a rate of PK-PD studies between adults and children would be interesting. However, since our dataset was created by use of a search filter specifically designed for trials in children (the "Clinical Trials in Children (CTC) search filter"), there are no studies of adults in our sample, and it is also not possible to add these.

We agree that more information on differences between the types of trials that are conducted in different age groups would make a useful addition to our article. We have therefore added Figure 3, showing the differences in studied health conditions or problems between different age groups.

Fig. 1 and 3 can be cancelled without affecting the information.

We have deleted Figure 1.
Concerning figure 3 (which is Figure 1 in the currently submitted revised version), we do believe that this figure contains valuable information. The fact that most trials report either generally on the collection of pharmacokinetic data, or only on measuring plasma or tissue concentrations, without giving much detail on which pharmacokinetic parameters will be calculated and reported is worrying and should be improved.

A few details about drugs and clinical conditions taken into account in retrived trials should be reported and discussed. A comparison with the EMA list of priorities should be useful.

We thank the reviewer for this useful suggestion. We have performed additional data collection on our study sample and collected the medicines that were studied in each trial as suggested (Web Only file 1). We added a comparison with the EMA list of medicines that were indicated to be a priority for pharmacokinetic research (Table 2). We adhered to the list from 2008, since it was relevant at the time we conducted our study. Additionally, we analysed whether the priorities from 2008 were still priorities in 2009 and 2010, to evaluate to which degree pharmacokinetic research had led to priorities being taken off the list.

The PK-PD lacking data is only a small part of the off-label scenario, even if authors underline often this association.

We agree, since our study focused on pharmacokinetic (and dynamic) data collection, we have put emphasis on these data in our introduction and discussion.

From the clinical point of view it should be interesting to know what these trials have produced or will produce for a better use of medicines in children in considered therapeutic conditions.

Although this is an interesting suggestion, we feel that linking the records in our sample to concomitant publications is beyond the scope of our study. Our research focused on highlighting the possibilities that clinical trials registration brings to comprehensively assess the state of ongoing research in a particular research area, in order to inform priority setting for this research.

Maurizio Bonati

Reviewer 2 (Helen Sammons) Comments for the Author...
Thank you for asking me to review this interesting paper. There are still few clinical trials of pharmacokinetics (PK) performed in children and this paper helps highlight this. It provides a clear review of the current situation of PK within research currently taking place.The methodology was clear and the data extraction robust. It gives new original data on the current research situation.

The conclusions on the topic and what the paper adds was sound and adds to the literature. My further comments for publication are below:

Major points:
1) A brief summary of the registers making up the ICTRP would be helpful and summary of the regions in the world they cover. This would allow the reader to put data presented later into perspective on where the clinical trials took place.

We have added this in the Methods section.

2) There were 1075 trials investigating a medicine, of which 245 collected PK data. The paper then breaks these down into regions of the world. It would have been helpful to not only see the percentage of total PK studies taking place in each region (table 1) but to be able to quantify this by the number of trials taking place in each region. So, for example, there were 15 PK trials in north africa which were 6% of the total PK trials. Were these all the trials in north africa or only a small percentage? This then needs to be quantified in the discussion. Is there just more research in N America, but is PK still neglected in the same proportion of studies?This needs quantifying in the article and abstract.

We thank the reviewer for this very good suggestion. We have performed additional data collection on all the trials that did not report to collect PK data in our study sample, and added the information that is requested (Table 1). Indeed, it sheds much more light on the types of trials in which PK data are collected. For example, the majority of trials collecting PK data recruit in Northern-America (77%). We have now found that although this is also the case for trials <u>not</u> collecting PK data, this percentage is much lower in this group (57%). The unequal geographical research distribution therefore appears to be a problem in general, but especially for trials collecting PK data.
Furthermore, we have also collected and added other additional information (study phase, sponsorship and age groups) for all trials <u>not</u> reporting PK data (Table 1).

Note: the numbers we report have changed slightly, because we chose to include trials researching several interventions (botulin injections and gene transfer vectors) that were previously excluded.

3) Did they review any of the trials not collecting PK data to see if it would have been relevant to do so?

We had not done this, but have added this analysis to our study. We searched the titles of all trials in our sample for the names of the medicines on the EMA 2008 list that we did not find any evidence of PK data collection for. We found that almost half of these medicines were studied in other trials, without any mentioning of PK data collection. We again thank the reviewer for her helpful suggestion; this strengthens our point that more PK research on the medicines that are on the EMA priority list must and can be undertaken.

4)Pharmacodynamic data in only 1/5 of PK studies was mentioned- this needs to be discussed along with the phase of the study as 27% were phase one and others did not specify.

We have plotted PD data collection against the different study phases, and have found that the distribution is similar to the distribution of PK data collection: a little less than half of the trials reporting PD data collection are phase 1 or phase 1&2. Our article does not report this distribution of collection of PD data among trials of different phases because we feel that it would distract from the other data we present.

Minor points:
1) i found Figure 2 difficult to read and i don't think it would reproduce easily in the journal.

Did this have to do with the quality of the figure, or the content? The content seems straightforward to us – the distribution of health conditions or problems studied in our dataset according to the WHO ICD-10 classification system.

2) The data only contained trials registered on the ICTRP, not the whole world. How inclusive is it?

The WHO ICTRP is the most inclusive database of clinical trials in the world, and at the time of this writing has information on more than 130,000 trials. It includes all records from ClinicalTrials.gov, but importantly also has information on the 15% of trials that are registered at other registries around the world (Viergever & Ghersi, 2011 PLoS ONE). Currently, 12 registries provide data on clinical trials to the ICTRP, located in Australia, China, Republic of Korea, India, Germany, Iran, Japan, the Netherlands, South Africa, Sri Lanka, the UK, and the US. Additionally, the International Committee of Medical Journal Editors (ICMJE) has endorsed registration of clinical trials at any Primary Registry that participates in the ICTRP (ICMJE, 2007).

Viergever RF, Ghersi D. The Quality of Registration of Clinical Trials. PLoS ONE. 2011 Feb ;6(2):e14701.

ICMJE. Update on Trials Registration: Clinical Trial Registration: Looking Back and Moving Ahead. 2007. http://www.icmje.org/update_june07.html

We would like to extend our gratitude to both reviewers for their careful consideration of our paper. Their suggestions have allowed us to make substantial improvements to our manuscript that shed more light on this important topic.

BMJ OPEN VERSION - REVIEW

REVIEWER	***Dr Helen Sammons***
REVIEW RETURNED	29-Jun-2011

THE STUDY	STROBE statement adhered to
GENERAL COMMENTS	This article is very important for progress in medicinines testing in the paediatric field. This revised version submitted here is much improved and now addresses the research question well and clearly.