Trial@home for children: novel non-invasive methodology for the pediatric clinical trial of the future

Kruizinga, M.D.

PART V

DISCUSSION

CHAPTER 16

Trial@home in pediatrics - A framework for remote and non-invasive data collection in pediatric clinical trials

MD Kruizinga, FE Stuurman, GJA Driessen, AF Cohen

The current pediatric clinical trial paradigm

Primary endpoints in pediatric clinical trials are currently very similar to those in adult trials[1], and focus on quantifying or counting hard endpoints like mortality, hospital admissions and length of stay. Additionally, biochemical biomarkers in serum are often measured to assess drug effects on a biochemical level. The occurrence of mortality and hospital admissions is rare thanks to the improvements in clinical care that have occurred in the last century, and adopting these as primary endpoints in clinical trials gives disproportional weight to rare events which most patients will not experience. Conversely, length of stay for many clinical conditions is short, and this duration only captures a small part of the clinical recovery trajectory that patients must undergo.

Besides hard endpoints, clinic-based assessments and composite scores that are related to one or multiple components of the disease clinical assessments are often used as outcome. Although such scores are useful, such scores incorporate a subjective component of the observer in the outcome, while at the same time providing a mere snapshot of disease activity in a clinical setting. As discussed in **Chapter 1**, a shift from hard endpoints towards value-based endpoints is a natural progression of the current clinical trial paradigm.[2] Value-based endpoints represent outcomes that patients care about, are suitable to detect individual outcomes and that are measured frequently in a patients' natural environment. These new objective biomarkers should be able to quantify if a drug or health care intervention *helps* individual patients, as opposed to that the drug *works* on a biochemical or organ system level.

Although one manifestation of value-based thinking in clinical trials is the adoption of patient reported outcome measures (PROS) in the form of questionnaires, PROS may not be the solution in pediatrics. Adequate report of PROS is reliant on adequate disease-understanding and a homogenous perception on what kind of symptoms constitute severe disease. These outcomes are extremely difficult to assess in a reliable way for young patients. Researchers often include the parent in the disease-scoring process, but this creates an additional subjective factor between the actual symptom severity and the PRO. Although PROs can be valuable and demonstrate the capability to characterize the *subjective* burden of disease, inclusion of *objective* monitoring techniques needs to be considered as well.[3]

Implementing more value-based endpoints in clinical trials will likely improve the insights obtained from all trials, but the concept is especially relevant for the pediatric clinical trial. Trials in pediatric populations are difficult to conduct due to several reasons, such as high proportion of non-consent resulting in low recruitment rates. Many reasons for non-participation in a study are unavoidable, such as concerns about a study drug, randomization, or blinding.[4] However, in that case it is only logical that steps must be taken to overcome other barriers as much as possible. One of the major other reasons of parents for non-participation in a clinical trial is that 'study logistics were too complicated or difficult',[5] and a perception by parents that a study may interfere with standard care may be a factor as well.[4] Additionally, other studies cite inconvenience for the child or the parents,[6] a lack of time, and a lack of interest as a frequent reason for nonparticipation.[7] Finally, many researchers report that concerns about the number of blood draws and burdensome logistics in general are a major barrier as well.[8]

Taken together, the factors described above invariably lead to the conclusion that a new perspective on the pediatric clinical trial is necessary, and many of the current barriers and limitations could be surmounted by adopting a remote clinical trial paradigm.

Towards remote data collection in pediatric clinical trials

Although there are numerous locations to monitor children, the most logical location is the home and school for several reasons. In these locations the child is naturally most comfortable, and the environment resembles 'real-world conditions' by definition, which cannot be achieved in hospitals or clinical research units. Since it is evidently unfeasible on financial and logistical grounds to send trained research personnel to the homes of every individual subject frequently, monitoring in the home must be achieved using different means. Technology in the form of digital biomarkers, also termed digital endpoints in the context of clinical trials, is a possible solution.[9]

Before digital biomarkers can be implemented in clinical trials, and eventually in clinical care, they must be rigorously validated to ensure they are fit-for-purpose. In **Chapter 2** we describe a stepwise approach towards endpoint selection, technical validation, and clinical validation of digital endpoints.[10] This approach can be applied to most digital measurements, algorithms, and devices. Technical validation means investigating whether the devices measure that what is claimed and focuses on the variability within- and between devices, the general usability, and the data processing pipeline. **Chapters 3-5**, provide examples of the technical validation of a novel mobile spirometer and smartphone-based

algorithms to detect crying- and coughing in children.[11] Clinical validation means investigating the endpoint in the target population, in this case pediatric patient groups. Important biomarker characteristics that are investigated during this process are the tolerability, repeatability, difference between healthy and ill groups, correlation with traditional endpoints and the description of health events. In **Chapters 6–11**, the clinical validation process of the remote measurement of physical activity, heart rate, forced expiratory volume in 1 second (FEV1), sleep duration, electronic PRO's (EPRO's) and tests incorporated in CHDR's NeuroCart® system is described in several conditions, specifically pediatric asthma, -pneumonia, -preschool wheezing, -obesity, -sickle cell disease, and ARID1B-related intellectual disability. *Table 1* lists the progression of the clinical validation process for various digital endpoints that were investigated in the current work. For several candidate endpoints, all preparatory work has been performed to be able to progress to the final, and arguably most important, step of the validation process: confirming the new candidate endpoint is able to detect the effect of new effective treatments.

Implementation of non-invasive pharmacokinetics can supplement remote clinical trials

Digital endpoints are a novel way to register what is traditionally termed the pharmacodynamics of drugs: the effect of the drug on the patient. However, the other cornerstone of clinical trials, pharmacokinetics (what the patient does to the drug), is traditionally evaluated in hospitals and clinical research units as well. Determination of pharmacokinetics is, among others, necessary in the event of target concentrations, e.g., in the case of antibiotic therapy, and when a specific PK-PD relationship is to be investigated. Traditionally this is done in blood samples, which is not easily transferred to the home environment. Although some advances have been made using dried blood spots, this still requires blood sampling and causes discomfort.[12,13] Developing novel non-invasive methods to obtain pharmacokinetic information may allow pediatric clinical trials to move completely towards the home. To achieve this, the sampling matrix of choice, which is currently plasma, must change to be able to obtain samples in a non-invasive manner at home. One such matrix is saliva[14,15], and in **Chapter 12**, we describe a framework to estimate plasma concentrations in individual patients based on obtained saliva samples with nonlinear mixed effect models and Bayesian maximum a posteriori (MAP) optimization. The framework is applied in practice for clonazepam and gentamicin in **Chapter 13** and **Chapter 14**.

Table 1. Progress of the validation process of (digital) endpoints investigated in the current work

Candidate endpoint	Technical validation	Clinical validation				
		Tolerability	Repeatability and effect modifiers	Difference healthy-ill	Correlation traditional endpoints	Description of health events
Physical activity	Yes[1]	Yes	Yes	Yes	Yes	Yes
Heart rate	Yes[1]	Yes	Yes	Yes	Yes	Yes
Cry (session) duration	Yes	-	-	-	-	-
Cough count	Yes	-	-	-	-	-
Pulmonary function tests	Yes	Yes	Yes	Yes	Yes	Yes
Sleep duration	Yes[1]	Yes	Yes	Varying	No	No
Sleep depth / wakeup count	Yes[1]	Yes	Yes	Varying	No	No
NeuroCart®	Yes[1]	Yes	-	Yes	Yes	-
EPRO's	Yes[1]	Yes	-	Yes	NA	Yes

1 Not investigated in the current work. Legend: blue: validation criterion was met in one or more clinical conditions. Yellow: criterion fulfillment was inconclusive at this point. Red: validation criterion was not met in the current studies. White: not investigated at this point, more research necessary.

In the framework, one could conduct a preparatory study in (young) adult subjects to determine the saliva:plasma correlation for a particular compound, perhaps already during phase I studies. The saliva:plasma relationship is variable across compounds, and therefore difficult to predict due to multiple factors, such as molecule size, polarity, protein binding, and salivary flow.[16] Although the relationship seems stable across several age ranges for multiple compounds, e.g. voriconazole, phenytoin, phenobarbital and lamotrigine,[14,17] extrapolation of the saliva:plasma relationship from adults to pediatrics is a major assumption of the framework, and we believe more confirmatory research is needed before this can be implemented. However, if the assumption is confirmed to be valid, future studies investigating the pharmacokinetics of new compounds in children could be based solely on salivary concentrations with back-calculation of plasma concentration based on the known saliva:plasma relationship determined in adults.

Other matrices that do not involve blood sampling can be implemented as well, given that drug concentrations in the matrix are predictable and related to plasma concentrations.[12,18] In **Chapter 15**, we describe an exploratory study investigating the use of exhaled breath condensate (EBC) in the field of pulmonary pharmacokinetics. However, EBC exhibited extremely high variability for both salbutamol and tobramycin, and the approach did not appear a promising avenue for further research.[19]

Pediatric disease areas that could benefit from digital biomarkers in clinical trials

The current work shows that digital endpoints can be applied to both chronic and acute disease. The largest focus has been on the respiratory diseases in this dissertation, and our results indicate that endpoints such as physical activity and heart rate are ready to proceed towards preliminary implementation in pediatric trials investigating pulmonary diseases. However, remote monitoring can be applied to other chronic diseases, such as obesity and sickle cell disease.

Additionally, there are many other unexplored disease areas that could potentially benefit from adopting the proposed framework. For example, pediatric dermatology trials could benefit from a combination of EPROS and objective digital endpoints, such as photos taken by parents. These photos can be transmitted to researchers for an objective assessment of the condition of the skin. The field of child- and adolescent psychiatry could include objective physical activity-, heart rate- and blood pressure monitoring to assess (adverse) effects of treatment in Attention Deficit Hyperactivity Disorder (ADHD). Trials in pediatric diabetes could incorporate non-invasive digital glucose monitoring devices,[20] combined with physical activity monitoring that may relate to quality-of-life related disease activity, and a heart rate sensor to monitor the cardiovascular consequences of the disease, similarly to what was shown in pediatric obesity in **Chapter 9**. Rheumatology is another example where continuous and objective monitoring could be beneficial beyond the inflammatory markers and patient reported outcomes that trials currently rely on. Finally, trials in rare (genetic) diseases, such as muscular dystrophies or neurological syndromes, will also benefit from adoption of the proposed framework in clinical trials. Patients are even more vulnerable compared to their peers with, and home-based trials would be the least invasive and therefore preferable. Considering the orphan drugs developed for these conditions are extremely high-priced, it is of paramount importance that rare disease clinical trials become more value-based and demonstrate that an expensive treatment translates to real value for patients in addition to, for example, biochemical-or cellular improvement.[21]

In short, there are many possibilities to move clinical trials towards the home and incorporate endpoints that are directly related to the manifestations of the disease that lead to significant burdens in patients. In addition, similar applications of the framework may be possible in numerous other conditions not listed here.

Beyond the clinical trial - Application of digital endpoints and non-invasive TDM in clinical care

The focus of the current work was on the validation of novel methodologies in clinical trials. However, a clinically validated digital endpoint has many potential applications in clinical care as well. Value-based medicine has been gaining popularity since the introduction of the concept by Michael Porter in 2010.[22] In clinical care, like in clinical trials, the goal of implementing more value in clinical care leads to the conclusion that personalized outcome measures are a necessary component of treatment effect evaluation. Objective digital endpoints combined with electronic patient reported outcomes may be suitable for this task.[2]

However, there are other applications of home-monitoring systems in clinical care that can supplement the current telemedicine paradigm. Although more popular in rural countries compared to The Netherlands, telemedicine allows patients to consult their doctors from the comforts of their home via a video- or phone call.[23] This is both more comfortable for the patient and potentially more cost-effective for the health care system, but the drawback is that the physician has no access to information obtained via the physical examination or additional tests. This drawback can be mitigated using digital measurements. For example, imagine the following: the physician has been given access to the 'personal health dashboard' by a patient with, for example, cystic fibrosis with worsening disease-activity. On this dashboard, the physician can see that physical activity, adjusted for weather and other variables, has been decreasing gradually towards levels that are on the low end of reference values, while nocturnal heart rate has been increasing at the same speed. Together with other parameters, such as periodical patient reported outcomes and pulmonary function tests, the holistic overview provided by the dashboard will make clear that a change in treatment is necessary to prevent further worsening of the disease towards a pulmonary exacerbation, which can be initiated promptly.

Looking further ahead, the improvement of artificial intelligence may eventually enable algorithms to analyze multiple sources of data to predict symptom severity during the upcoming days.[24] When the algorithm detects a high probability of worsening disease-activity, an intervention can be suggested to provide timely symptom relief.

Besides home-monitoring of disease-activity, the non-invasive pharmacokinetics based on saliva samples described in this dissertation can be extended to the field of therapeutic drug monitoring (TDM).[25] Although TDM is relatively uncommon in pediatrics, it

enables for precision-dosing in drugs where a clear target range in plasma concentrations is available, for example, in the case of several antimicrobials and anti-epileptic drugs.

Conclusion

The remote pediatric clinical trial paradigm, consisting of digital endpoints and non-invasive pharmacokinetic sampling, has the potential to transform pediatric clinical trials and pediatric clinical care. The process towards implementation is challenging and can only proceed after a rigorous validation process. The current work provides a roadmap towards selection, validation, and implementation of digital endpoints, and describes preliminary steps taken for several candidates. The digital endpoints investigated in this work fulfill several validation criteria in a range of clinical conditions and, combined with non-invasive pharmacokinetics, may move the pediatric clinical trial completely towards the home.

REFERENCES

1 Green DJ, Burnham JM, Schuette P, Liu XI, Maas BM, Yao L, McCune SK, Chen J, van den Anker JN, Burckart GJ. Primary Endpoints in Pediatric Efficacy Trials Submitted to the US FDA. J Clin Pharmacol 2018;58(7):885-890.

2 Kruizinga MD, Stuurman FE, Groeneveld GJ, Cohen AF. The Future of Clinical Trial Design: The Transition from Hard Endpoints to Value-Based Endpoints. 2019:371-397.

3 Kahan BC, Doré CJ, Murphy MF, Jairath V. Bias was reduced in an open-label trial through the removal of subjective elements from the outcome definition. J Clin Epidemiol 2016;77:38-43.

4 Hoberman A, Shaikh N, Bhatnagar S, Haralam MA, Kearney DH, Colborn DK, Kienholz ML, Wang L, Bunker CH, Keren R, *et al.* Factors that influence parental decisions to participate in clinical research: Consenters vs nonconsenters. JAMA Pediatr 2013;167(6):561-566.

5 Greenberg RG, Gamel B, Bloom D, Bradley J, Jafri HS, Hinton D, Nambiar S, Wheeler C, Tiernan R, Smith PB, *et al.* Parents' perceived obstacles to pediatric clinical trial participation: Findings from the clinical trials transformation initiative. Contemp Clin Trials Commun 2018;9(September 2017):33-39.

6 Institute of Medicine (US) Committee on Clinical Research Involving Children; Field MJ, Behrman RE, editors. Ethical Conduct of Clinical Research Involving Children. Washington (DC): National Academies Press (US); 2004. 5, Understanding and Agreeing to Ch.

7 Vermaire JH, Van Loveren C, Poorterman JHG, Hoogstraten J. Non-participation in a randomized controlled trial: The effect on clinical and non-clinical variables. Caries Res 2011;45(3):269-274.

8 Greenberg RG, Corneli A, Bradley J, Farley J, Jafri HS, Lin L, Nambiar S, Noel GJ, Wheeler C, Tiernan R, *et al.* Perceived barriers to pediatrician and family practitioner participation in pediatric clinical trials: Findings from the Clinical Trials Transformation Initiative. Contemp Clin Trials Commun 2018;9(September 2017):7-12.

9 Boehme P, Hansen A, Roubenoff R, Scheeren J, Herrmann M, Mondritzki T, Ehlers J, Truebel H. How soon will digital endpoints become a cornerstone for future drug development? Drug Discov Today 2019;24(1):16-19.

10 Kruizinga MD, Stuurman FE, Exadaktylos V, Doll RJ, Stephenson DT, Groeneveld GJ, Driessen GJA, Cohen AF. Development of Novel, Value-Based, Digital Endpoints for Clinical Trials: A Structured Approach Toward Fit-for-Purpose Validation. Pharmacol Rev 2020;72 (4)(October):899-909.

11 Kruizinga MD, Essers E, Stuurman FE, Zhuparris A, van Eik N, Janssens HM, Groothuis I, Sprij AJ, Nuijsink M, Cohen AF, *et al.* Technical validity and usability of a novel smartphone-connected spirometry device for pediatric patients with asthma and cystic fibrosis. Pediatr Pulmonol 2020;(June):2463-2470.

12 Jager NGL, Rosing H, Schellens JHM, Beijnen JH. Procedures and practices for the validation of bioanalytical methods using dried blood spots: A review. Bioanalysis 2014;6(18):2481-2514.

13 Kloosterboer SM, van Eijk E, van Dijk M, Dieleman GC, Hillegers MHJ, van Gelder T, Koch BC, Dierckx B. Feasibility of Dried Blood Spots in Children with Behavioral Problems. Ther Drug Monit 2020;42(4):648-651.

14 Hutchinson L, Sinclair M, Reid B, Burnett K, Callan B. A descriptive systematic review of salivary therapeutic drug monitoring in neonates and infants. Br J Clin Pharmacol 2018;84(6):1089-1108.

15 Patsalos PN, Berry DJ. Therapeutic Drug Monitoring of Antiepileptic Drugs by Use of Saliva. Ther Drug Monit 2013;35(1).

16 Haeckel R. Factors Influencing the Saliva/Plasma Ratio of Drugs. Ann N Y Acad Sci 1993;694(1):128-142.

17 Michael C, Bierbach U, Frenzel K, Lange T, Basara N, Niederwieser D, Mauz-Körholz C, Preiss R. Determination of saliva trough levels for monitoring voriconazole therapy in immunocompromised children and adults. Ther Drug Monit 2010;32(2):194-199.

18 Grumetto L, Cennamo G, Del Prete A, La Rotonda MI, Barbato F. Pharmacokinetics of cetirizine in tear fluid after a single oral dose. Clin Pharmacokinet 2002;41(7):525-531.

19 Kruizinga MD, Birkhoff WAJ, Esdonk MJ, Klarenbeek NB, Cholewinski T, Nelemans T, Dröge MJ, Cohen AF, Zuiker RGJA. Pharmacokinetics of intravenous and inhaled salbutamol and tobramycin: An exploratory study to investigate the potential of exhaled breath condensate as a matrix for pharmacokinetic analysis. Br J Clin Pharmacol 2020;86(1):175-181.

20 Ólafsdóttir AF, Attvall S, Sandgren U, Dahlqvist S, Pivodic A, Skrtic S, Theodorsson E, Lind M. A Clinical Trial of the Accuracy and Treatment Experience of the Flash Glucose Monitor FreeStyle Libre in Adults with Type 1 Diabetes. Diabetes Technol Ther 2017;19(3):164-172.

21 Cox GF. The art and science of choosing efficacy endpoints for rare disease clinical trials. Am J Med Genet Part A 2018;176(4):759-772.

22 Porter M. What is Value in Healthcare. NEJM 2010:2477-2481.

23 Greiwe J, Nyenhuis SM. Wearable Technology and How This Can Be Implemented into Clinical Practice. Curr Allergy Asthma Rep 2020;20(8).

24 Johnson A, Yang F, Gollarahalli S, Banerjee T, Abrams D, Jonassaint J, Jonassaint C, Shah N. Use of mobile health apps and wearable technology to assess changes and predict pain during treatment of acute pain in sickle cell disease: Feasibility study. JMIR mHealth uHealth 2019;7(12).

25 Soldin OP, Soldin SJ. Review: Therapeutic drug monitoring in pediatrics. Ther Drug Monit 2002;24(1):1-8.