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Data and digital tools in pediatric clinical trials

Aparito

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 6, NO. 4, 2021

TRANSLATIONAL PERSPECTIVE

Decentralized Clinical Trials

The Future of Medical Product Development?*

Gail A. Van Norman, MD

The Covid-19 pandemic disrupted many clinical trials that were potentially bringing new therapeutics to market—an additional untallied cost of the pandemic in lives and quality of life owing to delays in releasing potentially beneficial therapeutics to patients in need. A separate side-effect of the pandemic has been swift adoption of virtual interactions between physicians and patients to provide continuity of care while maintaining social distancing. This comes at a time of rapid advance- Currently, clinical trials for drug approval often already include decentralized elements, and DCTs often incorporate traditional design with decentralization of the patient/subject interactions (Central Illustration).

ADVANTAGES OF DCTs: SMALLER, FLEETER, CHEAPER, MORE DIVERSE?

DCTs may improve the logistics of conducting a

Pediatric RESEARCH www.nature.com/pr

SPECIAL ARTICLE OPEN

Improving clinical paediatric research and learning from COVID-19: recommendations by the Conect4Children expert advice group

Athimalaipet V. Ramanan[1,2], Neena Modi[3,4], Saskia N. de Wildt[5,6] and c4c Learning from COVID-19 Group

BACKGROUND: The COVID-19 pandemic has had a devastating impact on multiple aspects of healthcare, but has also triggered new ways of working, stimulated novel approaches in clinical research and reinforced the value of previous innovations. Conect4children (c4c, www.conect4children.org) is a large collaborative European network to facilitate the development of new medicines for paediatric populations, and is made up of 35 academic and 10 industry partners from 20 European countries, more than 50 third parties, and around 500 affiliated partners.
METHODS: We summarise aspects of clinical research in paediatrics stimulated and reinforced by COVID-19 that the Conect4children group recommends regulators, sponsors, and investigators retain for the future, to enhance the efficiency, reduce the cost and burden of medicines and non-interventional studies, and deliver research-equity.
FINDINGS: We summarise aspects of clinical research in paediatrics stimulated and reinforced by COVID-19 that the Conect4children group recommends regulators, sponsors, and investigators retain for the future, to enhance the efficiency, reduce the cost and burden of medicines and non-interventional studies, and deliver research-equityWe provide examples of research innovation, and follow this with recommendations to improve the efficiency of future trials, drawing on industry perspectives, regulatory considerations, infrastructure requirements and parent–patient–public involvement. We end with a comment on progress made towards greater international harmonisation of paediatric research and how lessons learned from COVID-19 studies might assist in further improvements in this important area.

Pediatric Research (2022) 91:1069–1077; https://doi.org/10.1038/s41390-021-01587-3

INTRODUCTION
Coronavirus-induced infective disease (COVID-19) has had a devastating impact on multiple aspects of healthcare. However, the pandemic has also triggered new ways of working, stimulated areas as well as parent patient involvement. These groups provide advice to academia and industry to design innovative paediatric clinical trials. Bringing the expertise of these experts together with experts from the regulatory agencies provided us

CORE CONCEPTS

In the wake of COVID-19, decentralized clinical trials move to center stage

Marcus A. Banks, *Science Writer*

In January 2021, New York's Northwell Health hospital system launched a clinical trial to learn whether the over-the-counter drug famotidine (also known as Pepcid) reduces the severity of COVID-19 in symptomatic patients who do not require hospitalization. The randomized trial began in response to anecdotal reports along with clinical studies showing that Pepcid benefited COVID-19 patients (1). But the trial had a twist: It was completely virtual; no visits to a research site required (2). In fact, it was the first fully virtual clinical trial for the health system. Northwell leaders say it won't be the last.

"COVID has sped up this process, and for the better," says Christina Brennan, VP for clinical research at Northwell's Feinstein Institutes for Medical Research. Brennan says that the initial design for the trial called for on-site visits, and that trial leaders pivoted upon realizing that prospective participants preferred to recuperate at home. The virtual model has enabled Northwell to recruit a more diverse set of participants than in its other trials, Brennan says, perhaps because on-site visits were not a barrier. Drugs (either Pepcid or placebo) were mailed to participants, and all laboratory draws were done at their home. The trial, which Northwell conducted in partnership with the Cold Spring Harbor Laboratory, NY, has concluded enrollment as of September 2021. Data analysis is ongoing.

Northwell is not alone in direct mailing—the practice became widespread during the pandemic. "That was basically ubiquitous. For all of our trials with oral therapy, we kept patients at home," says Keith Flaherty of Massachusetts General Hospital in Boston. Flaherty says a high priority in the early days of

'Opportunities provided by the digital environment play an increasingly crucial role in children's development and may be vital for children's life and survival'

Children reported that the digital environment afforded them crucial opportunities for their voices to be heard in matters that affected them'

United Nations Committee on the Rights of the Child, General Comment 25

*'..decentralised measures should improve the efficiency of future paediatric clinical trials**...**sponsors can reduce the trial burden to children and their families by incorporating flexibility in timing and number of hospital visits. This is important as missing school or social activities is one of the main self-reported burdens to children when participating in trials*

Improving clinical paediatric research and learning from COVID-19: recommendations by the Conect4Children expert advice group

Patient reported outcome assessment must be inclusive and equitable

Patient-reported outcomes are increasingly collected in clinical trials and in routine clinical practice, but strategies must be taken to include underserved groups to avoid increasing health disparities.

Melanie J. Calvert, Samantha Cruz Rivera, Ameeta Retzer, Sarah E. Hughes, Lisa Campbell, Barbara Molony-Oates, Olalekan Lee Aiyegbusi, Angela M. Stover, Roger Wilson, Christel McMullan, Nicola E. Anderson, Grace M. Turner, Elin Haf Davies, Rav Verdi, Galina Velikova, Paul Kamudoni, Syed Muslim, Adrian Gheorghe, Daniel O'Connor, Xiaoxuan Liu, Albert W. Wu and Alastair K. Denniston

Patient-reported outcomes (PROs) collected in clinical trials can provide valuable evidence of the risks and benefits of treatment from a patient perspective, to inform regulatory approvals, clinical guidelines and health policy. PROs are increasingly collected routinely in clinical settings, at an aggregate level for audit and benchmarking, for real-world evidence generation, and as an input or predicted output for clinical decision tools and artificial intelligence (AI) in health[1,2]. At an individual patient level, PROs can be used to facilitate shared decision making, screen or monitor symptoms, and provide timely care tailored to individual needs[3]. PROs are also increasingly used in value-based healthcare initiatives[4].

Efforts to capture and report PRO data should be inclusive and equitable, addressing the diverse needs of all patients with the condition of interest, including groups historically and currently underserved by research[5,6]. Issues of diversity, equity and inclusion (Box 1) have recently been highlighted in PRO ethical guidelines, which have identified a number of concerns to be addressed in PROs research[5].


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What We Do

Aparito brings clinical trials to patients and unlocks real-world data through mobile apps, video assessments & wearable devices.

We provide a patient-centric platform that integrates clinical & regulatory expertise to capture patient data and develop digital endpoints for hybrid and decentralized clinical trials to streamline the drug development process.

We digitize clinical trials.

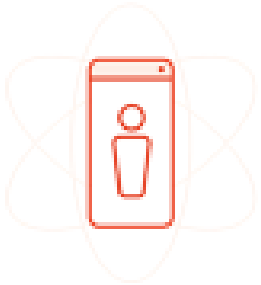
ISO/IEC 27001


atom5
Powered by
aparito

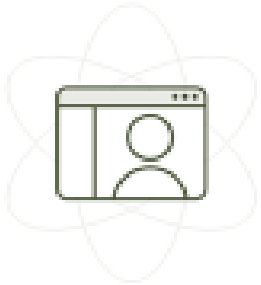
Atom5™ Features

Atom5™ is the clinical trial platform that offers Video Assessments, PROs, Telemedicine, EDC and eConsent.

All via one smartphone app.



Patient App & Dashboard

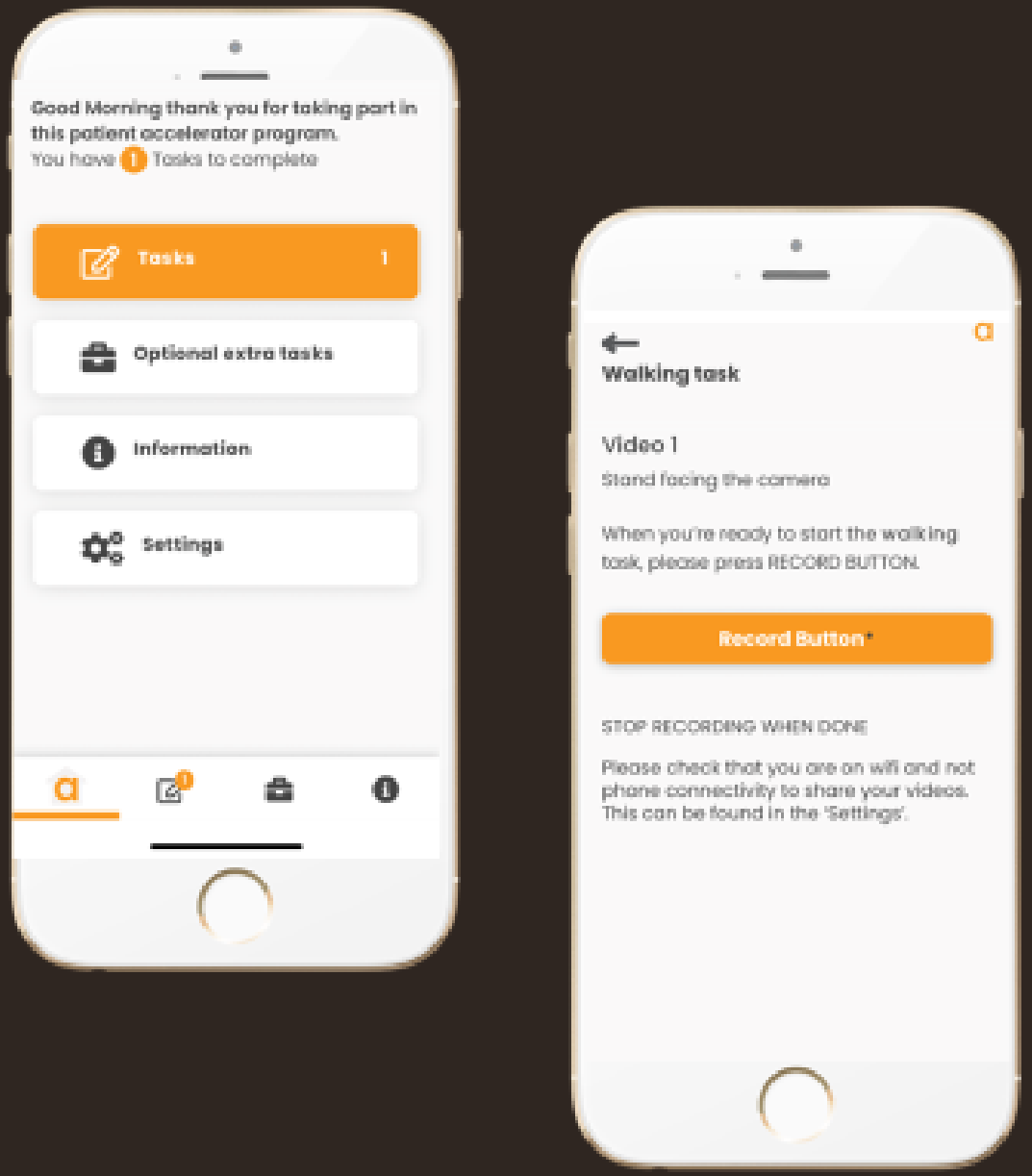


Clinical & Sponsor Portal

eCOA

Data Analytics

Regulatory Compliance



Patient App & Dashboard

Self Onboarding and eConsent

Patients can be onboarded and consent to the study remotely from their dashboard

Questionnaires

Customized or clinically valid digitized PROs

Tasks/Assessments

Allow patients to carry out assessments and perform task from the comfort of their home

Tasks & Assessments

Patients can perform tasks from the comfort of their home including our vTUG and SARA^{home} video assessments

Diaries

Allows patients to report a range of information from symptoms to medication dosage that are taking

Events

Allow patients to report adverse side effects in real-time

DocuSign partnership allows FDA compliant consent

eCOA

Video

Atom5™ video capture & analysis locates specific points on the body and computes the speed and trajectory of each movement to explore smoothness of motion and erratic patterns, enabling clinicians to assess features such as gait and posture.

ePRO

The PRO module is fully configurable and tracks actual patient outcome scores in addition to measuring each patient against the cohort. Our technology also has personalized branching for response-based data capture, making data capture more dynamic.

SARA^{home}

vTUG

Atom5™ Unique Offerings

SARA^{home}

The SARA tests were digitized as SARA^{home} in collaboration with DZNE.

SARA^{home} and conventional SARA are highly correlated.

vTUG

The video timed up-and-go (vTUG) test uses video capture and pattern recognition to enable objective, sensitive high frequency assessments

FEEDS

Feeding & Eating Evaluation viDeo analysiS (FEEDS) uses Atom5™ software to identify specific points on the face and hands and apply machine learning techniques to characterize age-dependent eating skill and technique.

Clinical & Sponsor Portal

Cohort View

Individual View

Clinician Portal

This allows the clinician to upload clinical data to the system, and communicate directly with individual patients

Dashboard

This allows the sponsor to view all patient data in an individual or cohort view with controlled access to the eCRF and eTMF

Real-Time

All patient captured data can be viewed in real-time to ensure quality and regular uploads

Verification With e-Link

PI can issue a specific link to the patient via their email which they need to access the e-consent

Patient Group Accelerator Programme

Aparito

Patient Group Accelerator Programme

The Aparito Patient Group Accelerator Programme (Accelerator) addresses the high unmet needs of patient communities by co-developing new digital biomarkers with patient groups.

Aparito launched the Accelerator programme in 2020 to provide an initiative where a company and patient community, with the support of patient advocacy groups, can collaborate as peers.

The Accelerator is designed to understand and ideally fulfil the patients' needs, by working closely with patient organisations and finding new endpoints that would be relevant to their specific conditions.

Aparito has a long-standing expertise in working with patient groups and won the EURORDIS Black Pearl Award 2022 for Health Technology!

EURORDIS *Black Pearl* AWARDS

DMD^{Home} Co-Creation Pathway

Location: UK

Condition: Duchenne Muscular Dystrophy

Duration: 12 Months

Overview and Challenges

Aparito worked with Duchenne UK to identify new digital biomarkers that could help provide a more accurate mapping of the transfer stage of the disease, i.e., progression from ambulatory to non-ambulatory, and that focused on upper limb strength, which was identified as important for patients in all stages of DMD.

Participants were put into cohorts to ensure that they weren't asked to complete a task which they were physically unable to do.

- Cohort one: ambulatory
- Cohort two: transfer
- Cohort three: non-ambulatory

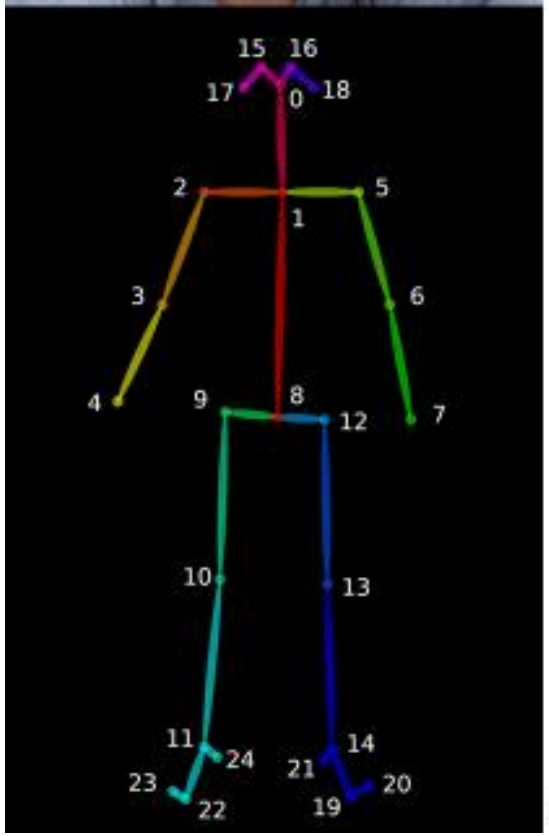
Our Approach

12 participants onboarded to app

Total of 62 videos uploaded, from 8 participants

52 videos (84 %) used in analysis (remaining do not include task, or completed task)

mediapipe.dev



github.com/CMU-Perceptual-Computing-Lab/openpose

Pose Estimation Software

OpenPose

Open-source software that detects points on the human body, hands and feet.

Output is a json file per frame, with pixel coordinates of each body point, and a confidence value associated with each point.

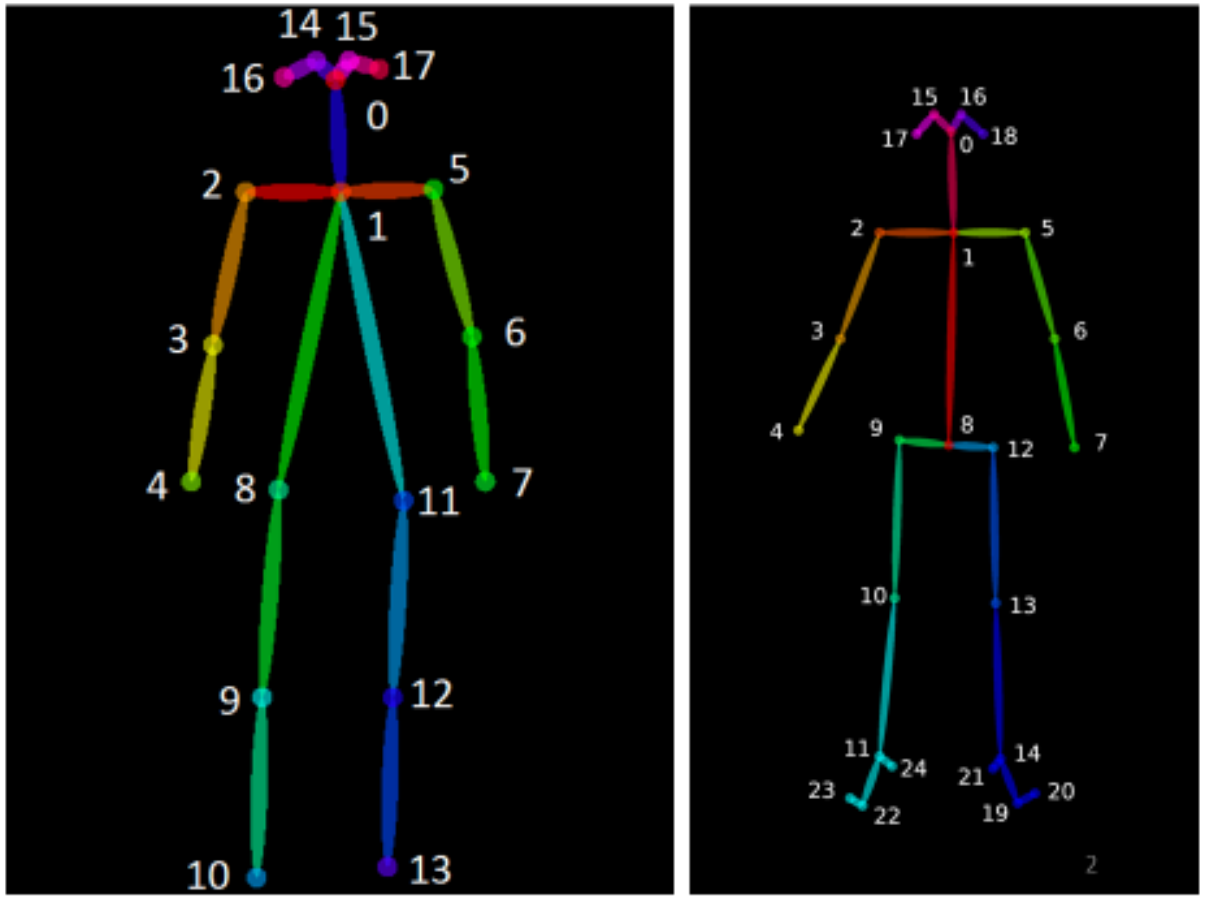
MediaPipe

Open-source framework for creating machine learning projects that analyse video data.

Many additional computer vision tools to pose-estimation e.g. segmentation, tracking.

openpose software

- OpenPose is open-source software that detects points on the human body, face, hands and feet.
- Can detect multiple people, or can restrict to specified number.
- Two different models - COCO (18pts) and Body_25 (25pts, includes feet).
- Output is a json file per frame, with pixel coordinates of each body point, and a confidence value associated with each point.
- Optional additional output is a copy of the original video, annotated with the identified body points.



The Patient - Patient-Centered Outcomes Research
https://doi.org/10.1007/s40271-021-00569-1

PRACTICAL APPLICATION

Time to See the Difference: Video Capture for Patient-Centered Clinical Trials

Elin Haf Davies[2,3] · Clare Matthews[2] · Adeline Merlet[4] · Martine Zimmermann[1]

Accepted: 12 December 2021

Abstract
Developing therapeutics for the treatment of rare diseases usually requires a strong understanding of the natural history of the disease. Often, it also requires the creation of novel assessment tools and clinical trial endpoints. In diseases where mobility is impacted, the use of video to capture the impact of the disease and the assessment of specific parameters, such as gait and stride length, can help design sensitive endpoints. Video as an assessment tool also allows the use of historical videos or videos filmed by non-experts outside of clinical settings. Given the increased use of telemedicine, the use of video may be a useful addition to clinical trial assessments. Two cases are presented: (1) the use of video in the development of asfotase alfa (Strensiq®) in hypophosphatasia is detailed as an example of the utility of this type of assessment in rare diseases; and (2) a home-setting video tool that was developed and validated ($SARA^{home}$) from a commonly used clinical scale (Scale for the Assessment and Rating of Ataxia [SARA]), allowing patients to record their own severity of ataxia. While there are certain limitations associated with video assessment, advancing technologies such as automated analysis and machine learning provide a tremendous opportunity for automated analysis of video recordings, reducing the bias associated with human assessment.

1 Introduction

of novel 'fit-for-purpose' assessment tools and clinical trial endpoints are frequently required.

m-Health in the management of paediatric epilepsy

Aparito

Medication Adherence in Practice

Medication Adherence as Observed Across a Pediatric Epilepsy Cohort within a Resource-Limited Setting

- Patients with a diagnosis of "refractory epilepsy" aged between 4-16years (median: 10) were recruited for the study
- Patients were required to download the study specific smartphone app powered by the Atom5™ software platform
- **Influencing and monitoring adherence:**
  - Prompts were provided for patients when their antiseizure medication (ASM) was due
  - Caregivers were able to state whether medication was taken or not, and provide reasoning
  - A medication adherence report was also completed in addition

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6

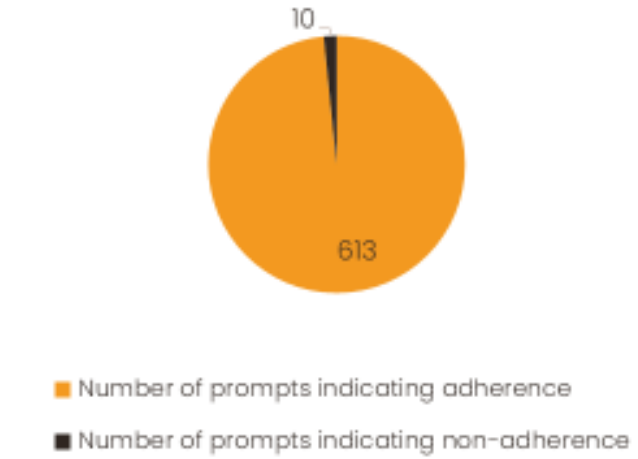
Medication Adherence in Practice

Medication Adherence as Observed Across
a Pediatric Epilepsy Cohort within a Resource-Limited Setting

"Yes, sometimes I do forget to give him (the medication)"

"I found the phone very helpful..it was reminding me when it was time for meds"

That is helpful because you can just capture events every day and you don't have to remember everything when you go for follow ups"



Reasons for non-adherence encompassed:

1. Forgetfulness (the most common factor)
2. Self perceived inefficacy (drug does not work)
3. No remaining drugs
4. The belief that it was making their child unwell (side effects)

Demonstrating the feasibility of digital health to support pediatric patients in South Africa
Epilepsia Open. 2021 Dec; 6(4): 653–662.

A qualitative study exploring caregivers' experiences, perspectives, and expectations for precision medicine in epilepsy in South Africa
Epilepsy & Behavior Volume 117, April 2021,

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A qualitative study exploring caregivers' experiences, perspectives, and expectations for precision medicine in epilepsy in South Africa

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ABSTRACT

Purpose: Successful implementation of innovative Precision Medicine initiatives in the management of children with complex epilepsy is largely dependent on the caregivers' engagement with the technology as well as its accessibility and acceptability. We investigated the feasibility of implementing these initiatives in the South African setting by gathering information on the caregivers' experiences, perspectives, and expectations for Precision Management of Epilepsy (PME) initiatives.

Methods: We purposively recruited 12 participants from a cohort of 40 caregivers of children with complex epilepsy recruited for a PME study attending Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa. Face-to-face semi-structured interviews were conducted using a pragmatic qualitative approach and themes were extracted using a thematic framework approach.

Results: All participants had ideas about the cause of epilepsy, but many did not think that epilepsy is a medical condition. There were several difficulties in adhering to medical treatment which was sometimes combined with traditional remedies and practices. Understanding of Precision Medicine in the context of research was limited and although participants were unclear about benefits, most were optimistic about the future. mHealth devices introduced new feelings and challenges for many participants. The four themes which emerged were: (1) Cause of epilepsy: uncertainty and conflicting views; (2) Need for healing; (3) PME mHealth devices; and (4) Feasibility of implementation of PME initiatives.

Conclusion: For Precision Medicine to be widely accepted and beneficial, how people understand the cause of epilepsy, difficulties in adherence to treatment, and personal experiences need to be addressed.

[A qualitative study exploring caregivers' experiences, perspectives, and expectations for precision medicine in epilepsy in South Africa]

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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia Open® Open Access

Demonstrating the feasibility of digital health to support pediatric patients in South Africa

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Funding information
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Abstract

Objective: Resources for management of epilepsy in Africa are extremely limited reinforcing the need to develop innovative strategies for optimizing care. Studies have shown that the prevalence of epilepsy in low- and middle-income countries is substantially greater than in more resourced countries. The objective of this report was to demonstrate that mobile Health (mHealth) technologies have the potential to improve the management of epilepsy in Africa.

Methods: The feasibility of technology-based home monitoring was investigated in an observational study of 40 children with refractory epilepsy or epilepsy associated with intellectual disability and/or behavior difficulties in South Africa. Technology-based home monitoring was implemented for six months. Physical activity, sleep, and heart rate were continuously monitored with a wearable device. Caregivers completed regular mobile Patient Reported Outcomes (mPROs) and reported seizures and ad hoc events using a dedicated app. Feasibility was assessed and descriptively

[Demonstrating the feasibility of digital health to support pediatric patients in South Africa]

Final points....


11:56
Episode 26: 'THE CLOUD' with Dr. Timothy...
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The Not Mini Adults Podcast - "Pioneers for Children's Healthcare and Wellbeing"
Episode 26: 'THE CLOUD' with Dr. Timothy Chou
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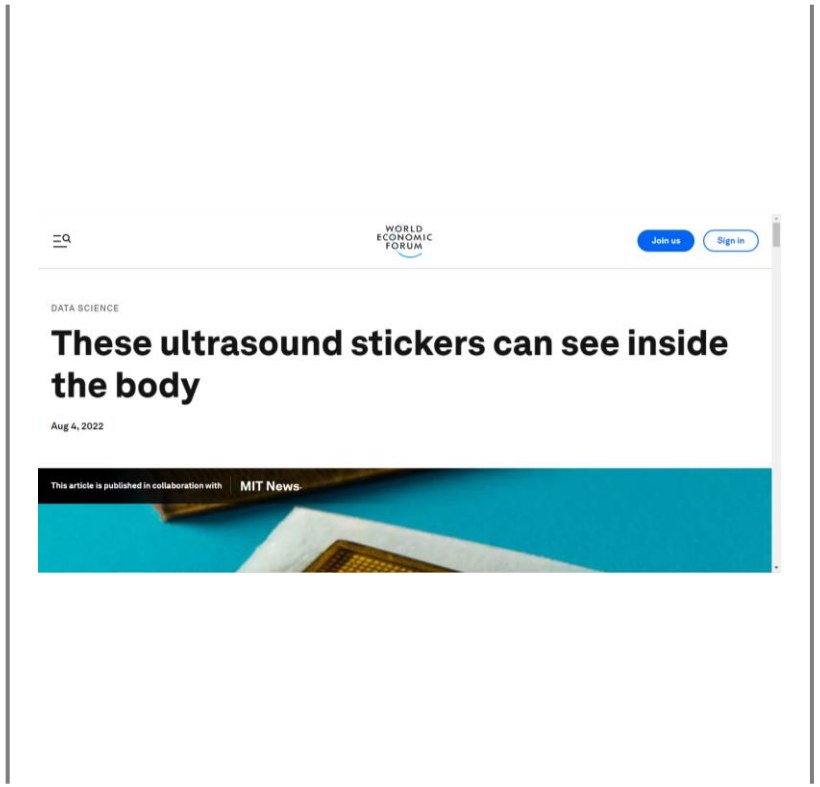
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These ultrasound stickers can see inside the body
Aug 4, 2022
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ELSEVIER
Using real-world data in pediatric clinical trials: Lessons learned and future applications in studies of persistent pulmonary hypertension of the newborn
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Real world data
Real world evidence
Persistent pulmonary hypertension of the newborn
ABSTRACT
Persistent pulmonary hypertension of the newborn (PPHN) is a complication of term birth, characterized by persistent hypoxemia secondary to failure of normal postnatal reduction in pulmonary vascular resistance, with potential for short- and long-term morbidity and mortality. The primary pharmacologic goal for this condition is reduction of the neonate's elevated pulmonary vascular resistance with inhaled nitric oxide, the only approved treatment option. Various adjunctive, unapproved therapeutics have been trialed with mixed results, likely related to challenges with recruiting the full, intended patient population into clinical studies. Recently, real-world data and subsequent derived evidence have been utilized to improve the efficiency of various pediatric clinical trials. We aim to provide recent perspectives regarding the use of real-world data in the planning and execution of pediatric clinical trials and how this may facilitate more streamlined assessment of future therapeutics for the treatment of PPHN and other neonatal conditions.

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