European Network of Paediatric Research at the European Medicines Agency

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SCIENCE MEDICINES HEALTH

COVID-19 impact on paediatric clinical trials, and how to overcome the challenges. Can some new approaches be taken forward for future paediatric trials? Industry perspective

2020 annual meeting of the members and Coordinating Group of the European network of paediatric research at the EMA (Enpr-EMA)

September 28th 2020

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COVID-19 pandemic has been on-going for almost 10 months

- 32,505,202 cases recorded worldwide (as of 25Sept.2020); Approx 1.7% in children*
- Travel and hospitals must be avoided for safety reasons
- Most of children enrolled in clinical trials are affected by severe disease requiring routine clinical care
- National healthcare systems had to adapt rapidly at operational and infrastructure levels
- New standards arise for patients remote monitoring and decentralised clinical trials

The fundamentals of high quality pediatric research should not be compromised, particularly pertaining to research governance

*Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020, CDC

COVID-19 Impact on Paediatric Clinical Trials

1. On-going clinical trials:

   Challenges related to operational aspects (lack of resources at sites, access,…) but also lack of validated age-appropriate endpoints with remote data collection

2. Most companies had to put their trial on hold to avoid change of endpoints

3. However COVID-19 is here to stay and industry is adapting

Impact on Paediatric Clinical Trials: Endpoints

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Motor Domain

Instruments	Equipment	Additional Apple Product	Remote Administration
9-Hole Pegboard Dexterity Test	• 9-Hole Peg Test Kit	--	**Cannot be done** unless the equipment is in front of the participant
Grip Strength Test	• Hand Dynamometer	--	**Cannot be done** unless the equipment is in front of the participant
Standing Balance Test	• iPod -Protective case • Balance Pad (e.g., AIREX) • Gait Belt with Velcro (e.g. Scott) • Sanitary booties	iPod (5th generation or later) Balance Pod App (Free App Store download	**Cannot be done** unless the equipment is in front of the participant
4-Meter Walk Gait Speed Test and 2-Minute Walk Endurance Test	• Measuring tape • 2 Cones • Diagram for Walking Course (*Appendix 6 of the Administration Manual*) • Colored masking tape for walking course	--	**Cannot be done remotely**

- Unless the participant can interact with equipment, 9-hole pegboard, grip strength, and standing balance cannot be administered.

Cognition Domain

Instrument	Equipment	Cognition Supplemental Materials	Remote Measure Created	Remote Administration
Picture Vocabulary	None	None	Yes, see **Appendix A** for supplemental Test instructions	**Can be administered remotely**; see supplemental notes and Appendix A
Picture Sequence Memory Test	None	None	Yes, see **Appendix A** for supplemental Test instructions	**Can be administered remotely**; see supplemental notes and Appendix A
List Sorting Working Memory Test	Bluetooth Wireless Keyboard	NIH Toolbox List Sorting Working Memory Test Examiner Answer Sheet	None	**Can be administered remotely**; see supplemental notes below
Flanker Inhibitory Control and Attention Test	None	Home Base	None	**Cannot be administered remotely** unless the iPad & home base are in front of the participant [scoring is based on timing accuracy]
Dimensional Change Card Sort Test	None	Home Base	None	**Cannot be administered remotely** unless the iPad & home base are in front of the participant [scoring is based on timing accuracy]
Pattern Comparison Processing Speed Test	None	None	None	**Cannot be administered remotely** unless the iPad is in front of the participant [administration is based on timing accuracy]
Oral Reading Recognition Test	Bluetooth Wireless Keyboard	Oral Reading Recognition Test Training and Certification Materials	None	**Can be administered remotely**; see supplemental notes below
Oral Symbol Digit Test (Supplemental)	None	Oral Symbol Digit (OSD) Form (for Participant)	None	**Cannot be administered remotely** as OSD form cannot be emailed or left with the participant. If examiner cannot ensure that the OSD form has been returned or destroyed.
Auditory Verbal Learning Test (Supplemental)	None	None	None	**Can be administered remotely**; see supplemental notes below

Source: NIH toolbox for remote administration

Impact on Paediatric Clinical Trials: Operational

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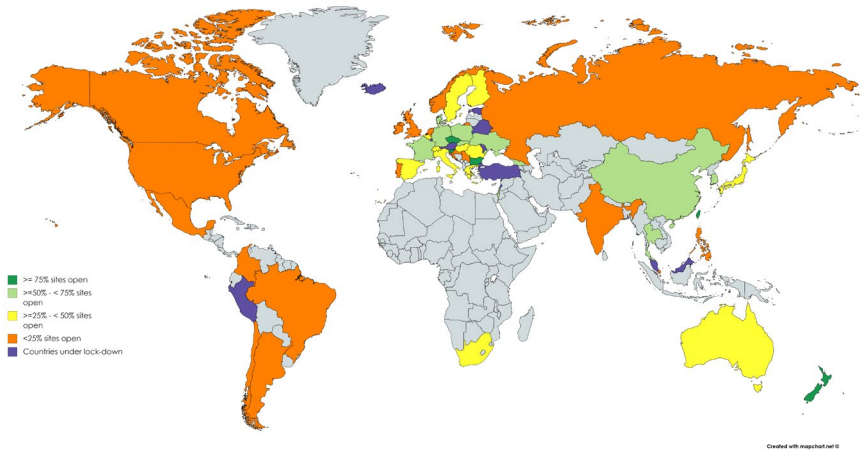
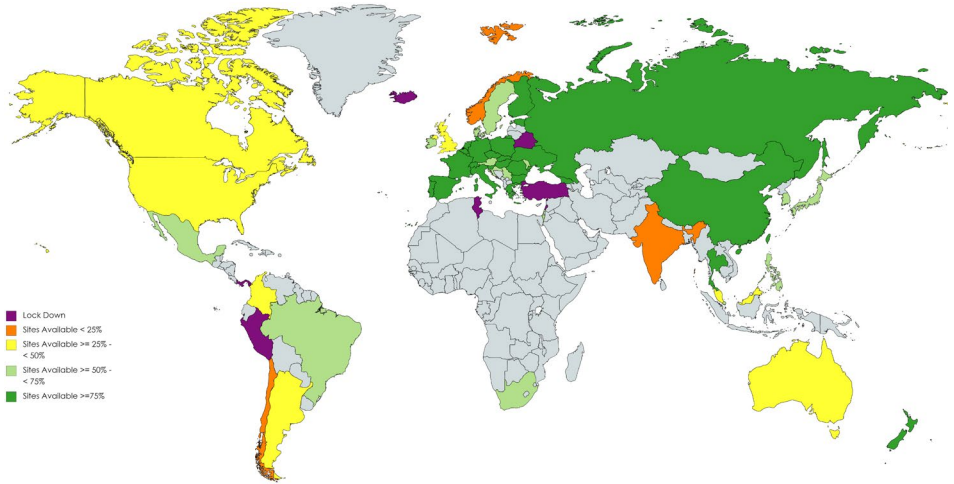
Availability of Sites, 5 June 2020



Availability of Sites, 21 Sept 2020



From virtual visit to Decentralized trials - A spectrum of solutions

- Decentralized Clinical Trials (DCTs) ensure safety while enabling CTs participations
- Telemedicine with technology wearables, sensors, videos can complement traditional CTs
- Patients Centric and minimise burden on children and families

- However, for paediatric research fully DCTs may not always be possible (e.g: subcutaneous infusion that requires specialised staff)
  - Option of hybrid trials with combination of home and sites visits (budget for paediatric needs to be planned in advance)

Paediatric Phase II trial in Duchenne Muscular Dystrophy. Treatment with a monoclonal antibody during COVID-19 pandemic (1/2)

- Challenge faced: Non-ambulatory children to visit clinic every 2 weeks for 1,5-5 hrs infusion
- Solution Implemented: Home Health Care for children to receive treatment at home
  - Nurse assigned by Home Health Care provider
  - Nurse met courier at patient's home
  - Nurse transmitted data to site at end of visit
  - Investigator at the site entered data into EDC (including AEs)
- Outcome: Positive
  - Parents/Care givers and patients highly satisfied. Alleviated study fatigue especially for long term treatment
  - Eliminated the fear parents had to have to travel to sites during the COVID-19 pandemic. No missed visits
  - Positive impact on patient retention (especially for a study over several years)
- Problem faced at a few sites
  - Not all sites allow Home Health Care when the drug is to be prepared by site pharmacy (Explore central pharmacy)

Paediatric Phase II trial in Duchenne Muscular Dystrophy. Treatment with a monoclonal antibody during COVID-19 pandemic (2/2)

- Lessons learned from Phase II trial:
  New approaches implemented for the phase III trials
  - Protocol for the Phase III trials
    - Home Health Care included
  - Explore option remote SDV
    - Access to data will ensure patient safety and data integrity
  - Remote monitoring
    - No impact in case of denied access to sites
    - Allows CRAs to dedicate more time to data review
    - Reduction in trial costs (40% clinical costs are travel costs)

Paediatric Phase III trial in T2DM, 24 countries

- Challenge faced
  - Patients not attending their face to face visits
- Solution Implemented: Changes in trial conduct
  - IP direct dispensation to the patients
  - Established guidance for sites
    - Reporting PDV, AEs/SAEs, what critical data MUST be collected, how to protect the critical endpoints (guidance for storing lab samples at site), how to manage delayed study visits
  - Monitoring of upcoming patient study visits, and discussion with the sites how best to manage COVID-19 impact
  - New study metrics
  - Protocol amendment to include the guidance on managing delayed study visits and study design change
- Impact of COVID-19 pandemic on the trial
  - Increased recruitment time (9 months for 76 patients)

Clinical Trial Protocol Planning under COVID-19 Pandemic

Impact to Study Visits

- Conversion of physical visits into phone or video visits
- Postponement or complete cancellation of visits
- A temporary halt of the trial at some or all trial sites
- Suspension or slowing down of recruitment of new trial participants
- Extension of the duration of the trial
- Postponement of trials or activation of sites that were not initiated
- Specific COVID-19 updates to data collection tools

Impact to Study Conduct

- COVID-19 does not warrant protocol waivers
- Receipt of IP to be documented
- Protocol deviations be used to document changes to visit conduct
- Process deviations to be used at a study level
- Statistical Analysis Plan Updates
  - Consultation with regulators when extensive changes are required

Protocol Deviations

- Visits / Endpoints
  - Missing
  - Replaced by alternatives
    - Virtual visits or by TC
    - Local rather than central labs
  - Extended visit windows
- Information needed per trial participant
  - Outline specific limitation caused by COVID-19 pandemic (why)
  - Impact on trial participant
  - Specify relationship to COVID-19
  - Duration of COVID-19 impact
    - Period between the first PD related to COVID-19 and the day before the 1st visit after the last PD related to COVID-19

ALL impacted visits/endpoints recorded

COVID-19 Pandemic - Operational Mitigations

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RISKS	MITIGATIONS			
Face2Face meeting travel	Video / Webex			
SIVs restricted	Telephone	Virtual tours	Pre-ship supplies months early	Delay activations
Enrollment checks needed	Mandate GCP compliance	Confirm safety monitoring	Demand PI obligations upheld	Ensure durable IP supply	Delay enrollment
Data entry backlog	Review metric weekly	Critical safety data entry at minimum	Ensure SAE/DLT reporting	
IMVs restricted	Remote monitoring	Prioritized Off-site Interim Monitoring Visits	Central analytics	JReview
IP supplies unreliable	Send extra now	Ship direct to patient	Alternate co-med vendors	
Need for pt engagement	Patient education	Permit local clinic labs	Pt reported symptoms (NCI PRO-CTCAE)	Patient feedback
Disease response compliance	Endpoint compliance	Treatment management consistent		
Specialty lab samples	Have sites hold to ship later if possible	Batch ship before courier or receipt issues	If results for eligibility, prepare to delay	If results for immediate pt management

SIV = Site Initiation Visit
PI = Principal Investigator
IP =Investigational Product
SAE = Serious Adverse Event
IMV = Interim Monitoring Visit

Remote Source Data Verification

- Limitations Observed at Some Sites
  - Poor availability of accessible electronic medical records (majority of source documents still on paper).
    Need progressive digitalization of medical records
  - Limited equipment at the sites: Webcam availability limited, site staff to use personal mobile
  - Limited availability of site staff due to the emergency status

Study Conduct Shift

From hospitals …

… to connected devices

New Operational Approaches to be Taken Forward for Future Trials

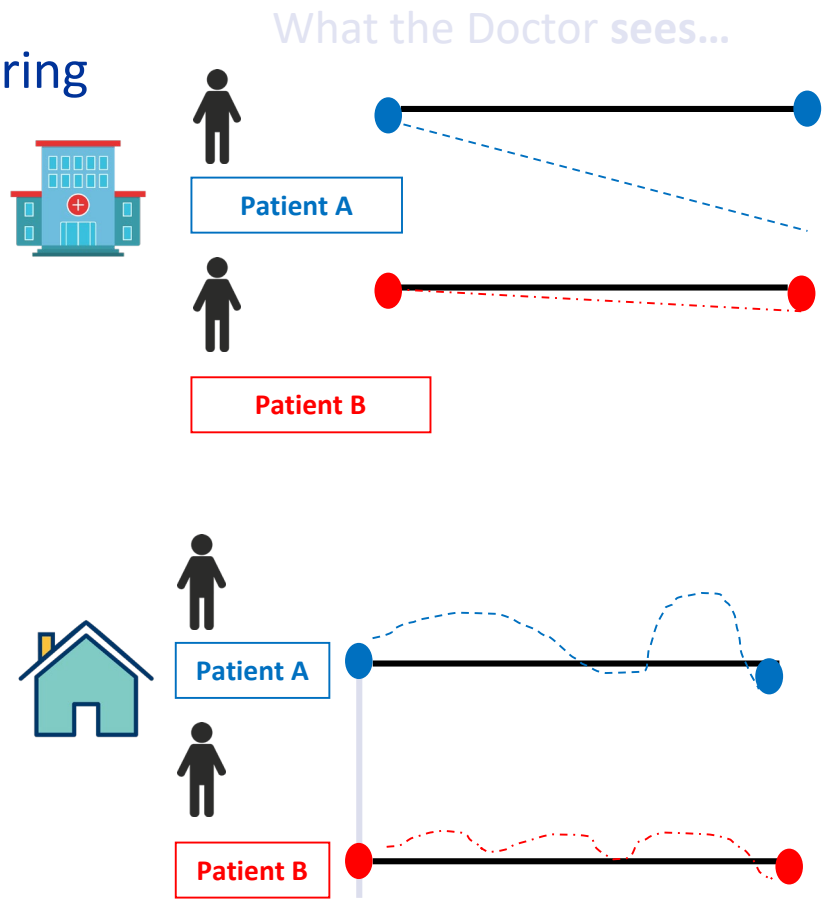
- Move towards remote processes, e.g.,
  - Remote SIVs, OIMVs, COVs
  - Remote SDV through EMR
    - Full oversight and timely clear understanding of the situation at site
    - Benefits patient safety
  - Automatic transfer from health records to eCRF
  - eConsent, ePRO ….
- Direct-to Patient IMP delivery
  - Ensures treatment continuity
- Implementation of Home Health Care
  - Limits burden for paediatric participants and their families/caregivers, increases retention
- Pragmatic approach from Regulatory Authorities
- Focus on the essential: Patient safety and well-being. Evaluation of risk vs benefit

Endpoints to be Adapted for Remote Monitoring

Insights that can be captured via the mobile phone in real time.

Examples of Patient Generated Data are:

- Patient Reported Outcomes
- Performance Outcomes measured via *video or wearable*
- Caregiver Burden
- Patient preference
- Medication adherence



Need for regulatory pathways adapted to the use of technology in paediatric CTs

Building the Ark Before the Flood

Thank you for your attention

Further information

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