Innovation in Pediatric Therapeutics Development: Integrating an Effective Clinical / Regulatory Strategy

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Disclosure

- I am an employee of Bayer Healthcare, LLC based in the United States
- I have worked in the Pharmaceutical industry primarily focused on developing medicines for children for 28 years
- I am sharing my personal views with the audience today

Topics for Discussion

- Key regulatory policy themes relating to pediatric clinical research and implications for rare disease research…
- Novel design elements for pediatric trials in rare diseases – experience when socializing these concepts with Health Authorities around the globe…
- Does clinical development always HAVE to begin in adults? Lessons learned and a few recent examples…
- Can we further improve our approach when we strive for concordant guidance with global Health Authorities? A Sponsor's perspective…

Key regulatory policy ‘themes’ relating to pediatric clinical research

- Successful effectuation of pediatric clinical trials is challenging -- a non-trivial proportion of pediatric clinical trials never achieve enrollment goals

- Key challenges with pediatric and rare Dx clinical trials:
  - Children can’t advocate for themselves – parents / caretakers and informed consent
  - Protracted enrollment periods – especially in large US academic centers
  - LT follow up challenges – most especially in the US
  - Sponsor may fail to secure concordant perspectives with major Health Authorities – then what?

- Pre-competitive public / private partnerships – critical component going forward

- Advocacy groups have become much more active and scientifically sophisticated

- A transition from ‘have to’ to ‘want to’ – Legislation / Health Authority & ecosystem driven…

- In part due to a rapidly advancing, industry-wide pivot towards regenerative medicines (with a significant focus on monogenic / congenital Dx’s)

The Emerging Field of Targeted Regenerative Therapeutics: Field State of the Art per *Clintrials.gov*

	Emerging Stem Cell Based Therapies	Emerging Gene Based Therapies
Total *Unique Identifiers…*	> 9400	> 10600
That are *Interventional*	> 8200	> 7500
And are *Sponsored Trials*	> 2300	> 2870
And *Enroll Children*	435	494
And *Allow Enrollment of Infants*	180	164
Example/s	HUCD-Mesenchymal SC's for the Tx of BPD	AAV-based monogenic Dx targets: SMA, DMD, IRDs

Megatrends Providing ‘Tailwind’ For Field

- Rapid advancement in technology – delivery / precision targeting
- Legislative changes – IRA, etc.
- Regulatory incentives that are meaningful for Sponsors, eg. RMAT
- Diagnostic improvements: Advancement of Rapid Whole Genome Sequencing (rWGS) – early in life diagnosis with high diagnostic yield
- Life cycle strategy focusing on younger (youngest possible?) patients
- Health Authorities and Sponsors ‘learning as we go’ – most especially when children are the prioritized patient population

Novel design elements for pediatric trials in rare diseases

- Traditionally designed pediatric clinical trials are operationally challenging – most especially in severe, rare disease populations and in the United States
- Poorly understood natural disease progression in many rare pediatric diseases
- Consider use of adaptive study designs to seamlessly (and more rapidly) transition to pivotal trial/s
- Consider use of 'fit-for-purpose' RWD sources:
  - EMRs
  - Patient registries
  - (Recent) Peer-reviewed publications
  - *Natural History Studies*
- From RWD to RWE -- Potential use of RWE in clinical trials:
  - Using large (RW) datasets and AI/machine learning tools to identify 'patient endotypes'
  - Synthetic / external control arms

Does clinical development always HAVE to begin in adults?

- Short answer -- no
- Traditional pediatric development (must do) has typically followed adult development with an approach where the Sponsor uses pharmacokinetic and pharmacodynamic data collected in pediatric patients to extrapolate efficacy
- Over the last decade, we have observed examples of therapeutics being development primarily / exclusively for children, eg.:
  - iNO MAX®
  - ZOLGENSMA®
  - ELEVIDYS®
- Pediatric-disease focused regenerative medicine programs will continue to grow
- Including adolescents in adult pivotal trials

Can we further improve our approach when we strive for concordant HA guidance?

- Short answer -- yes

- Global Health Authorities (FDA, EMA, PMDA, Health Canada, etc.) have significant broadened cross-Agency exchanges in recent years regarding mutually relevant pediatric development topics and more recently, the regenerative medicine topic
  - Pediatric Cluster
  - Joint Scientific Advice

- While helpful in some respects, there is an opportunity to improve the efficiency of the approach and related timely communication to Sponsors, eg.
  - Sponsors currently do not participate in Pediatric Cluster exchanges
  - Joint scientific advice typically requires a protracted period for scheduling, advice may be discordant and advice in not binding
  - Can we reimagine the approach with the goal of harmonization?

- Continued expansion of the (disease specific) rare disease public / private partnership ecosystem – all parties ‘at the table’

A few related closing comments…

- Incentives matter in the thesis – Pediatric Rare Disease Designation
  - Short interval to (every ~ 4 year) sunset makes Sponsors think twice
- Legislative changes sometimes have unintended consequences – IRA and orphan Dx
- We have access to a MASSIVE amount of RWD across the US EHR ecosystem – if only it were interoperable:
  - *Biggest challenge* in any rare pediatric disease studies is patient identification and trial enrollment
  - Pre-feasibility – where the patients are
  - Expedited patient identification via AI-based search
  - Creation of regulatory grade disease progression models as a basis for better treatment development and as potential RWD (synthetic) comparator arms in clinical studies
- To accomplish this, we must address remaining national level hurdles (via collaboration with ONC/HHS):
  - Increasing the level of data interoperability through application of existing standards (HL7 FHIR) and collaboration with corresponding Accelerators (eg. Vulcan)
  - Encourage patients entering a hospital system to provide informed consent to use collected data for future research topics – in an anonymized fashion (to assure data privacy)

Thank you for your attention

Q&A