Computational Health Informatics Program

Harvard-MIT Center for Regulatory Science

Boston Children's Hospital

HARVARD MEDICAL SCHOOL

DRUG DEVELOPMENT FOR PEDIATRIC RARE DISEASES

Florence T. Bourgeois, MD, MPH

Associate Professor of Pediatrics | Harvard Medical School

Director, Harvard-MIT Center for Regulatory Science | Harvard Medical School

Division of Emergency Medicine & Computational Health Informatics Program | Boston Children's Hospital

General considerations for pediatric clinical trials

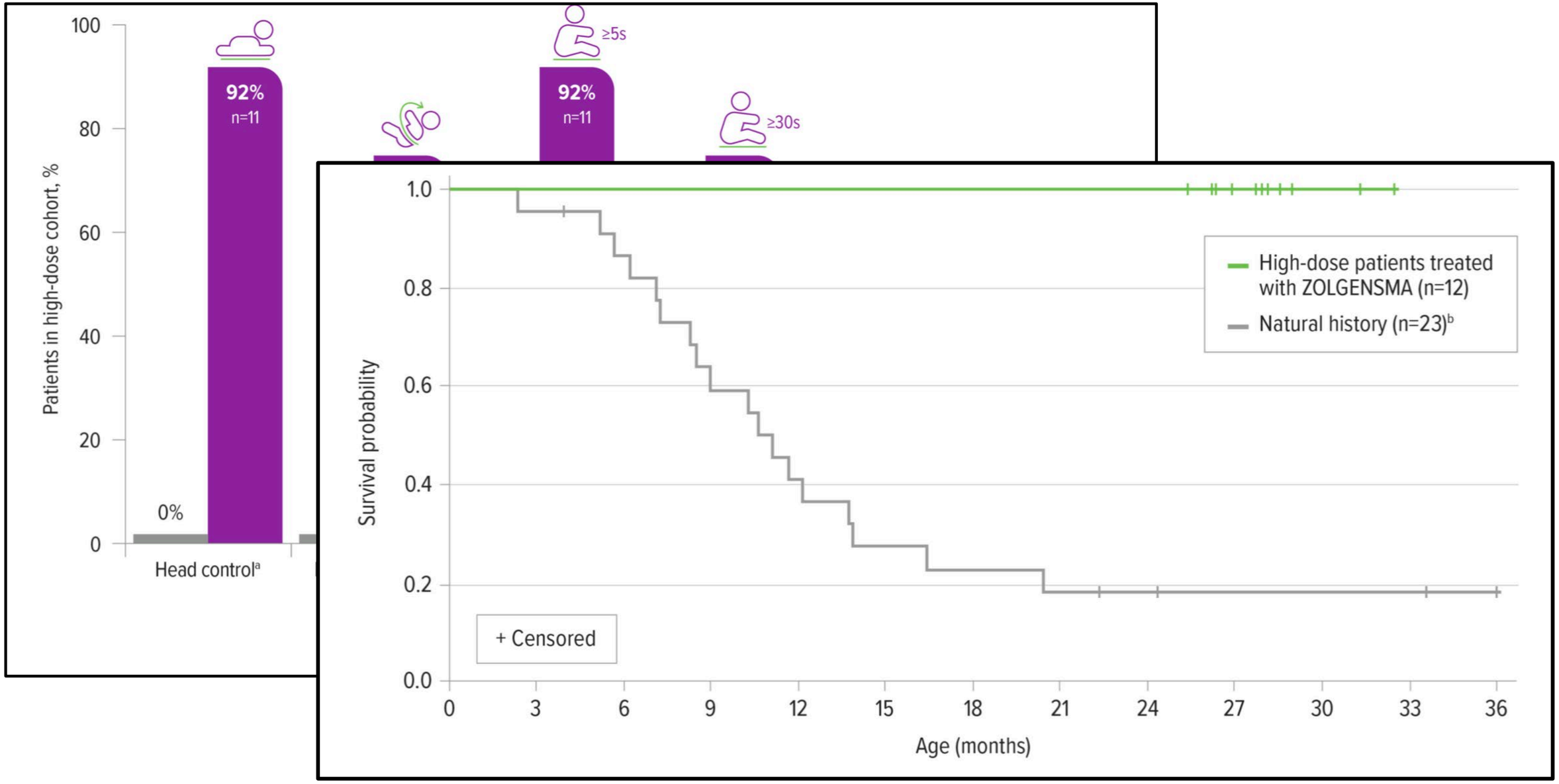
- Must balance **obligation to conduct trials** in children to ensure evidence-based treatments with **need to protect a vulnerable population** from unknown risks related to trial participation
- Pediatric patients should only participate in a clinical trial if the scientific objective **cannot be met through study of individuals who can give informed consent** (i.e. adults)
- Special protections:
  - Without the prospect of direct clinical benefit, participation **may not involve greater than minimal risk**
  - If there are risks, these must be justified by **anticipated direct benefits to the child**, at least as favorable as any available alternatives

Unique challenges in pediatric clinical trials for rare diseases

- **Small patient populations** that are often geographically dispersed
- Limited number of **research centers and clinical experts** to guide trial design and conduct
- **Phenotypic diversity** within the affected population
- **Lack of validated endpoints**, outcome measures (e.g. biomarkers), and measurement tools
- **Natural history** often not well understood
- **No precedent** for drug development for a specific disease

Example of pediatric rare disease drug approval

- **Spinal muscular atrophy (SMA)**
  - prevalence of ~1-2 per 100,000 persons in the U.S.
  - for SMA type 1, prevalence of 0.04-0.28 per 100,000 persons in U.S.
  - Median life expectancy of ~1 year for children with SMA type 1
- **Onasemnogene abeparvovec-xioi (Zolgensma)**
  - approved by FDA in 2019
  - treatment of patients < 2 years of age with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene


Patients in high-dose cohort, %
100
80
60
40
20
0
0%
92%
n=11
92%
n=11
≥5s
≥30s
Head control[a]
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
3
6
9
12
15
18
21
24
27
30
33
36
Age (months)
High-dose patients treated with ZOLGENSMA (n=12)
Natural history (n=23)[b]
+ Censored

Pediatric specific regulatory programs – US and EMA

	U.S. - BPCA	U.S. - PREA	EU - Pediatric Regulation
Year	2002	2003	2006
Development	Optional	Mandatory	Mandatory
Timing	As early as end of phase 2	End of phase 2	End of phase 1
Product type	On and off-patent	On patent	On patent
Orphan products	Included	Exempt	Included
Reward	6-month exclusivity	None	6-month exclusivity

Pediatric specific regulatory programs

- Pediatric Rare Disease Priority Review Voucher
  - Went into effect in 2012
  - A sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product
  - Voucher can be sold (estimated market value = $100M)

→ Sunsets on September 30, 2024 – should the program be renewed?

RACE Act

- Research to Accelerate Cures and Equity (RACE) for Children Act
  - Went into effect in 2020
  - Modified PREA to give FDA authority to require pediatric studies for oncology products with a molecular target potentially relevant to a pediatric cancer
  - Limited to oncology products
  - Orphan products are NOT exempted

→ Should this approach be extended to other therapeutic areas?

Take-aways

- Unique considerations for pediatric clinical trials with additional challenges related to pediatirc rare disease research and drug development
- Several regulatory programs in place in the US and EU to address pediatric rare disease drug approvals
  - Potential modifications and/or extensions to be considered
- Approval rates for pediatric orphan products are encouraging

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Thank you!

Florence Bourgeois, MD, MPH

florence.bourgeois@childrens.harvard.edu

@ftbourgeois

References

- https://www.fda.gov/files/science%20%26%20research/published/Ethics-of-Pediatric-Product-Development-%28May-19-20--2011%29.pdf
- Medpace - https://vimeo.com/683962149
- https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0931-2
- https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0671-8
- https://www.zolgensma-hcp.com/clinical-experiences/str1ve-trial-efficacy/
- https://www.fda.gov/media/127961/download?attachment