Industry Perspective on Master Protocols and Platforms

FDA Sept 23, 2016 Workshop on Pediatric Master Protocols

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Presentation Outline

• Why Master Protocols?
• Challenges in Pediatric Oncology Drug Development
• Mechanism-of-Action Based Drug Development in Pediatric Oncology
• The iMATRIX Trial Concept and Its Master Protocol
• Opportunities & Challenges
Master trials: finding the right trial for the patient
integrate predictive biomarkers, enable simultaneous study of multiple targeted agents
across different tumor types in small populations of patients

Modern Oncology
Drug Development

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Master trials have multiple potential advantages

*increased access for patients, optimized and cost-effective study conduct*

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**Efficiency of screening**
- Large population of patients screened
- Up-front screening for multiple biomarkers
- Common platforms for biomarker assessment
- Reduced screen failure rate

**Expanded patient eligibility**
- Access to many options
- Higher chance of being placed into a treatment arm (among many)
- Availability of treatments for uncommon-rare genotypes/subsets

**Increased speed of drug development**
- Flexibility of closing and opening studies
- Single protocol
- Require fewer patients to be enrolled
- Vast clinical trial networks
- Shared control groups (recruitment time)
- Faster trial activation

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**Reduced cost of drug development**
- Shared cost
- Cost savings from common trial infrastructure and single screening process
- Failures are early and cheap
- Shared control groups (trial costs)

**Greater/better options for patients**
- Sponsors can pursue disease areas of interest not supported by internal programs
- Patients are more likely to receive treatments that deliver meaningful benefit (See I-SPY 2)

**Accelerated drug approval**
- Harmonized regulatory processes (e.g., single IND, etc.)
- Expedited review processes

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*Key reference: Seminars in Oncology: October 2015, 42(5), 724–730*
Children with cancer also need access to new and more efficacious therapeutic options

Challenges

High **attrition rate in adult drug development** contributes to lack of early access to investigational drugs.

Pediatric oncology drug development is largely based on adult drug development programs. The majority of **pediatric tumors are rare and distinct entities** from those seen in adults.

Multiple programs compete for a **limited patient pool** and for academic collaborators.

**Reactive obligatory** vs proactive voluntary approach.

**Limited market incentives**

Opportunities

Leverage **pediatric expertise**

**Match and prioritize** molecules for pediatric cancers based on **target or mechanism of action** of the drug.

Identify **new targets** in pediatric cancer.

Increase efficiencies with **innovative trial designs**.

Greater multi-stakeholder **collaboration** and sharing of information.
Mechanism of action or target-based drug development in pediatric oncology

- Target-based drug development has largely benefited adult oncology patients. Drug development in children need to keep pace with advances in science.

- Adjust the focus of pediatric oncology drug development to the many pediatric diseases for which there are no adult counterparts, rather than exclusively on the tumor types being investigated in adults.

- Limit initial plan proposals to early phase pediatric clinical research, and defer discussion of pivotal trials until early-phase pediatric data is available.

- Greater cooperation and collaboration between stake-holders to prioritize new molecules based on mechanism of action or target of the drug.

- Standardize targeted approaches to ensure consistent interpretation by health authorities and industry for widespread adoption and sustainability.

- Ultimately, preserve and match children with rare tumors to the most promising therapies.


Robin Norris & Peter Adamson, Challenges and opportunities in childhood cancer drug development, Nature Reviews Cancer 12, 776-782 (November 2012)
The iMATRIX trial concept: preserve and match children with rare tumors to the most promising therapies

An innovative pediatric oncology clinical trial platform to investigate several drugs in multiple tumor types

Adult Phase 1-2 Studies

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The ultimate goal is to allow for molecule & disease prioritization within the regulatory framework

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**Objective:** one sponsored pivotal study per molecule in one disease supported by clinical evidence and feasibility assessment (extensive consultation with Academic Community and HAs)

- Advance to pivotal trial
- Available for supported research
- No further development

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iMATRIX trial status update

*rapid accrual across a number of pediatric tumor types*

- **Single molecule clinical studies** for atezolizumab and cobimetinib in several pediatric cancer tumor types have been initiated.

- **Master Trial proposal** is currently being evaluated by the FDA and EMA
  - Joint FDA and EMA *Parallel Scientific Advice* and EMA Qualification procedure meeting on 31st August, 2016
  - Strong encouragement from the agencies to continue with the iMATRIX Trial efforts

- **Outreach Efforts for future Multi-Sponsor Master Trial** collaborations to enable industry to fulfill its mission of addressing unmet need for children with cancer and to provide rare patients with the most promising therapies.
iMATRIX Master Protocol and Drug-specific appendices

An open-label, multi-center, Phase I/II Study, to evaluate the PK, safety, tolerability and efficacy of drugs in the treatment of relapsed or refractory pediatric tumors with known or expected pathway involvement.

Study 1
iMATRIX Master IND/CTA

Master Protocol +
Drug A appendix

Drug B appendix

Drug C appendix

Drug D appendix

Drug “n” appendix

Master IND/CTA for multiple drugs in multiple tumor types

IND/CTA amendments to add or remove drugs

Study 2
New IND/CTA for Pivotal Study(ies)

best molecule: tumor match

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The iMATRIX trial and its master protocol

*an ongoing experiment with obvious opportunities… and some remaining challenges*

**Challenges**

- New concept in pediatrics for national HAs and IRBs, lack of centralized review process may impact **review timelines**
- Complex design and quality oversight may complicate protocol & amendment **authoring and study start up**
- Operational benefits may only be seen when **a critical number of molecules** are available on the iMATRIX
- **Combinations** may require separate IND/CTA
- Ultimately, **actionable molecular targets may be rarer in children** compared to adults, limiting the impact of predictive biomarkers

**Opportunities**

- Target true **unmet needs** in childhood cancer
- **Evidence-based** identification of optimal tumor type(s) for each molecule
- **Consistency** of data collection, analysis, and interpretation
- **Operational efficiency** of trial conduct: same sites, accelerated implementation, optimization of costs
- Ultimately, provide a **standardized framework** for patient-centric development that preserves study participants and matches children with rare cancer to the most promising therapies **across industry’s portfolio**
Paradigm shifts are urgently needed in pediatric drug development

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<th>Isolated development</th>
<th>Harmonized across industry</th>
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<td>Reactive, late</td>
<td>Proactive, early</td>
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<td>“Stick and carrot”</td>
<td>Pediatric-centric</td>
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<td>Molecule-based in disease context</td>
<td>Mechanistic, biomarker-based in disease and molecule context</td>
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Doing Now What Patients Need Next