Welcome

Gilles Vassal, ACCELERATE
an international multistakeholder organisation working to solve the central challenges in the development of innovative anticancer medicines for children and adolescents

OUR NAME IS OUR MISSION
Since last year........
PHARMACEUTICAL STRATEGY FOR EUROPE

- Learning from COVID-19, towards a crisis-resistant system
- Ensuring accessibility and affordability of medicines
- Supporting sustainable innovation, emerging science and digitalisation
- Reducing medicines shortages and securing strategic autonomy

#EUPharmaStrategy

Revision of Pediatric and Orphan Regulations
Europe's Beating Cancer Plan: A new EU approach to prevention, treatment and care
2020 Nobel chemistry prize for gene-editing tool (CRISPR-cas9)
New approved anticancer medicines in 2020

• 22 new medicinal products for cancer (18 drugs, 3 diagnostic imaging, 1 BLA)
• 4 with a pediatric indication

• 11 new medicinal products for cancer
• 2 with a pediatric indication

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Brand</th>
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<tbody>
<tr>
<td>Selpercatinib</td>
<td>Retevmo</td>
<td>RET+ thyroid cancer &gt;12 years</td>
</tr>
<tr>
<td>Selumetinib</td>
<td>Koselugo</td>
<td>Neurofibromatosis type 1 &gt;2 years</td>
</tr>
<tr>
<td>Tazemetostat</td>
<td>Tazverik</td>
<td>Epithelioid sarcoma &gt;16 years</td>
</tr>
<tr>
<td>Naxitamab</td>
<td>Danyelza</td>
<td>High-risk neuroblastoma &lt;1 year</td>
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<td>Entrectinib</td>
<td>Rozlytrek</td>
<td>NTRK+ tumors &gt;12 years</td>
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</table>
FDA approves crizotinib for children and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma

January 14, 2021

10 years!
Since last year in
ACCELERATE staff: the dream team

Teresa de Rojas, MD, PhD
Scientific Coordinator
(joined Oct 2020)

Michael Vranken, MPharm
Policy & Communication Administrator
(joined Sep 2020)

Andrea Demadonna, M.S.
ACCELERATE Coordinator
ACCELERATE Steering Committee

Academia
- Steven DuBois
- Pam Kearns
- Elly Barry
- Hubert Caron
- Lynley Marshall
- Lia Gore

Industry
- Mark Kieran
- Darshan Wariabharaj

Patients Advocacy
- Leona Knox
- Patricia Blanc
- Susan Weiner
- Nicole Scobie

Regulatory Bodies
- Koen Norga
- Dominik Karres
- Gregory Reaman
- Alberto Pappo

Intuitu personae
- Jeffrey Skolnik
- Raphaël Rousseau

SIOP Europe CEO
- Samira Essiaf

ITCC President / ACCELERATE Chair
- Gilles Vassal

PSF Oversight Committee Chair/Senior Advisor
- Andy Pearson
No blame, no shame
Generate data and find solutions
Together
Pediatric strategy forums

2017
PSF#1
ALK inhibition

2018
PSF#2
Mature B-cell lymphoma

PSF#3
CheckPoint Inhibitors

2019
PSF#4
Acute Myeloid Leukemia

2020
PSF#5
Epigenetic modifiers

2021
PSF#6
CAR T cells

PSF#6
TKI in sarcomas
ACCELERATE 360°

Fostering Age Inclusive Research
Fit For Filing
Long Term Follow Up
International Collaboration
Real World Evidence
ACCELERATE Educational Webinars

Everything you always wanted to know about Strategic & Regulatory Science in pediatric oncology

We are launching a series of ACCELERATE Educational Webinars in 2021

• Multi-stakeholder experts will explain complex topics in interactive sessions
• Young (and not-so-young) researchers, pharma representatives, patient advocates and regulators are all welcome to join this exciting new ACCELERATE adventure!

More information coming soon... STAY TUNED!
326 attendees
Breakout sessions - 5:45pm – 7:30pm CET
You’ll find your group in the email sent on 2 February 😊

BkS 1. How to facilitate pediatric development of medicines that are terminated in adult cancer development?
Co-Chairs Group A
Peter Adamson, Sanofi
Davy Chiodin, DayOne Therapeutics

Co-Chairs Group B
Delphine Heenen, KickCancer
Hubert Caron, Roche

BkS 2. Tissue-agnostic evaluation of compounds in rare sub-groups
Co-Chairs Group A
Steven DuBois, Dana-Farber
Michael Cox, DayOne Therapeutics

Co-Chairs Group B
Lynley Marshall, The Royal Marsden
Greg Reaman, FDA

BkS 3. RACE for children act – early impressions and what are the best metrics to measure its success
Co-Chairs Group A
Susan Weiner, Children's Cause
E. Anders Kolb, Nemours AIm duPont Hospital for Children

Co-Chairs Group B
Cormac Owens, Children's Health Ireland at Crumlin
Elly Barry, Pfizer

BkS 4. Incentives for drug development including first-in-child development and small biotech companies
Co-Chairs Group A
Beth Fox, St. Jude
Raphaël Rousseau, Gritstone Oncology

Co-Chairs Group B
Nick Bird, Solving Kids' Cancer Europe
Jeffrey Skolnik, Inovio Pharmaceuticals

BkS 5. How to prioritise developments in specific areas of pressing unmet pediatric needs?
Co-Chairs Group A
Lia Gore, Children's Hospital Colorado
Nicole Scobie, Zoé4life

Co-Chairs Group B
Leona Knox, Solving Kids' Cancer Europe
Dominik Karres, EMA
A new work stream

Access to medicines outside clinical trials

in the paediatric precision oncology landscape and capturing data
9TH ACCELERATE PAEDIATRIC ONCOLOGY CONFERENCE 4-5 FEBRUARY 2021 VIRTUAL

WWW.ACCELERATE-PLATFORM.ORG

@ACCELERATE_cure

Supported by:

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER
International precision oncology landscape and the needs of access to medicine

Julia Glade Bender, *Memorial Sloan Kettering Cancer Center*
Paediatric multidisciplinary, clinical sequencing program

- Sample acquisition and processing (Surgery, Pathology)
- Educate and consent patient families (Oncology)
- Analysis pipeline (Pathology, Bioinformatics, Computational Biology)
- Molecular tumor board (Oncology, Pathology Genetics, Scientists)
- Return of results (Oncology, Genetics)
- Clinical decisions (Oncology)
Comprehensive, multiomic, molecular tumour profiling

- Cancer variants
- Germline variants
- Cancer-specific mutations
- Copy number variation
- Translocations
- Gene (variant) expression
- Expression vs reference
- Tumor classifiers
### Challenge: Paediatric access to matched targeted therapies

<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>Tumor Types</th>
<th>Potentially Actionable Findings</th>
<th>Matched Targeted Therapy</th>
<th>Germline Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEDS-MIONCOSEQ</td>
<td>U Michigan</td>
<td>102</td>
<td>High Risk (HR) Solid, CNS, Heme</td>
<td>46%</td>
<td>14 (33%)</td>
<td>10%</td>
</tr>
<tr>
<td>BASIC3</td>
<td>Baylor</td>
<td>150</td>
<td>New Diagnosis Solid, CNS</td>
<td>39%</td>
<td>ND</td>
<td>10%</td>
</tr>
<tr>
<td>iCat</td>
<td>Dana Farber CUIMC, UCSF DC Childrens</td>
<td>101</td>
<td>HR Solid</td>
<td>34%</td>
<td>3 (10%)</td>
<td>ND</td>
</tr>
<tr>
<td>INFORM</td>
<td>German Ca (20 centers)</td>
<td>57</td>
<td>HR Solid, CNS Heme</td>
<td>50%</td>
<td>10 (38%)</td>
<td>4%</td>
</tr>
<tr>
<td>PIPseq</td>
<td>Columbia/ CHONY</td>
<td>101</td>
<td>HR Solid, CNS, Heme</td>
<td>38%</td>
<td>6 (16%)</td>
<td>14%</td>
</tr>
<tr>
<td>MBB</td>
<td>Institut Curie</td>
<td>60</td>
<td>HR Solid, CNS</td>
<td>40%</td>
<td>6 (26%)</td>
<td>ND</td>
</tr>
</tbody>
</table>
Potential pathways to drug access

Clinical trials

• Biomarker driven “basket trials”: Pediatric Molecular Analysis for Therapy Choice (MATCH, NCT03155620); European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours (ESMART, NCT02813135)

• Histology restricted “umbrella trials”: Next Generation Personalized Neuroblastoma Therapy (NEPENTHE; NCT02780128)

• Biomarker cohorts in industry or consortium sponsored single agent trials

• Other early phase trials (with or without enrichment strategies)

Non-study options: N-of-one

• Off label use of commercially available agents

• Single patient use (SPU) investigational new drug (IND)

• Compassionate use or expanded access “protocols”
Fig. 2: Overview of national and international precision medicine programmes for paediatric oncology.

Drug access
- Basket trials in relapsed or refractory cancers across multiple tumour types:
  - ESMART (INFORM, MAPPYACTS and IETHER patients)
  - INFORM2 (INFORM, MAPPYACTS, IETHER and ZERO patients)
  - Pediatric MATCH (US patients only)
- Disease-specific umbrella trials
- Molecular aberration-driven single agent targeted therapy across tumour types
- Compassionate drug access
- FDA-approved drugs

Molecular profiling platforms
- Panel sequencing: SNV and INDEL, CNA, Germline, Fusions (pediatric MATCH)
- WES: SNV and INDEL, Germline, CNA (MAPPYACTS)
- WGS: SNV and INDEL, CNA, SV and fusions, Germline
- RNA-seq: Fusions, Gene expression (ZERO)
- Methylation 850K array: Tumour classification
- Gene expression arrays: Gene expression

Basket Trials: Not every disease is equally responsive, even with the exact same mutation of interest.
12 year old with inflammatory myofibroblastic tumor; ALK negative.

Novel VCAN-IL23R fusion

Predicted fusion protein:
- Extracellular domain of VCAN (versican)
- IL23 C-terminal extracellular domain, transmembrane domain and intracellular signaling domain
- Activate intracellular signaling by phosphorylation of JAK2

?? Ruxolitinib
Failures not reported and reasons not well understood: Wrong target, wrong drug, wrong dose?

• Ruxolitinib: Pediatric recommended phase 2 dose
  • 50 mg/m² dose PO BID (Loh et al, Ped. Blood and Cancer, 2013)

• FDA Approved dose for adults with myelofibrosis
  • Starting dose 20mg twice daily (Maximum Dose 25 mg PO BID)

• Patient BSA= 1.5m²; Calculated dose 75mg twice daily
  • Insurance company authorized 25mg twice daily

• Patient progressed:
  • Was the tumor driven by the translocation?
  • Can the drug effectively suppress signaling?
  • Were adequate plasma levels achieved?
Compassionate use, expanded access, SPU

• Need a willing partner: A pharmaceutical company willing to provide both the agent and dosing recommendations

• Labor intensive: Write a “protocol for one”, submit to the national regulatory body (e.g. FDA) and institutional IRB/ Ethics Board

• Unfunded mandate: Institution provides research pharmacy, clinical oversight and research compliance/ SAE reporting as if a phase 1 trial

• Lost opportunity for data collection: Represents a “single patient treatment plan” not a “research study”
  • Clinical data is captured (but generally no PK, PD or other ancillary studies)
  • IND information is not routinely consulted or “used” to support licensing
SPECC1- RET driven fibrosarcoma 21 days after Selpercatinib

Compassionate use: signal of efficacy

### BEFORE
- Left lower lobe: 4.9 x 3.6 cm
- Left renal: 6.3 x 4.9 cm
- Multiple lesions in the right posterior parietal, temporal, and occipital lobes

### AFTER
- Left lower lobe: 3.6 x 2.3 cm
- Left renal: 3.1 x 2.6 cm
- (No longer evident)
Preliminary data as prelude to a focused clinical trial

Activity of the Highly Specific RET Inhibitor Selpercatinib (LOXO-292) in Pediatric Patients With Tumors Harboring RET Gene Alterations

Michael V. Ortiz, MD; Ulrike Gerdemann, MD; Sandya Govinda Raju, MBBS, PhD; Dahlia Henry, BA; Steve Smith, BS; S. Michael Rothenberg, MD, PhD; Michael C. Cox, MHS, BCOP, PharmD; Stéphanie Proust, MD; Julia Glade Bender, MD; A. Lindsay Frazier, MD; Peter Anderson, MD, PhD; and Alberto S. Pappo, MD

A Study of Oral LOXO-292 in Pediatric Patients With Advanced Solid or Primary Central Nervous System Tumors (LIBRETTO-121; NCT03899792)

Selpercatinib for the Treatment of Advanced Solid Tumors, Lymphomas, or Histiocytic Disorders With Activating RET Gene Alterations, a Pediatric MATCH Treatment Trial (NCT04320888)
## National Profiling Programmes

<table>
<thead>
<tr>
<th>Institutions</th>
<th>N</th>
<th>Patients</th>
<th>Matched w/ FU data</th>
<th>Received MTT</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFORM</td>
<td>&gt;1300</td>
<td>Pediatric HR cancer</td>
<td>525</td>
<td>149 (28%)</td>
<td>van Tilburg <em>et al.</em> ASCO, 2020 LBA10503</td>
</tr>
<tr>
<td>MAPPYACTS</td>
<td>500</td>
<td>&lt;18 years RR cancer</td>
<td>197</td>
<td>56 (28%)</td>
<td>Berlanga <em>et al.</em> AACR, 2019 CT081</td>
</tr>
<tr>
<td>SMPaeds</td>
<td>233</td>
<td>≤24 years solid</td>
<td>57</td>
<td>4 (7%)</td>
<td>George <em>et al.</em> Eur J Cancer. 2019</td>
</tr>
<tr>
<td>iCat2</td>
<td>388</td>
<td>≤30 years HR solid</td>
<td>170</td>
<td>25 (15%)</td>
<td>Corson <em>et al.</em> AACR Peds, 2019; A28</td>
</tr>
<tr>
<td>Pediatric MATCH</td>
<td>422</td>
<td>1-21 years HR solid, CNS</td>
<td>112</td>
<td>39 (35%)</td>
<td>Parsons <em>et al.</em> ASCO, 2019 10011</td>
</tr>
<tr>
<td>Zero Childhood Cancer Program</td>
<td>252</td>
<td>Pediatric HR cancer</td>
<td>134</td>
<td>43 (32%)</td>
<td>Wong <em>et al.</em> Nat Med 2020</td>
</tr>
<tr>
<td>PROFYLE</td>
<td>338</td>
<td>≤29 years HR cancer</td>
<td>NA</td>
<td>NA</td>
<td>Grover <em>et al.</em> AACR, 2020 5413</td>
</tr>
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</table>
Gaps in international precision oncology landscape

• Programmatic, centralized international repository for genomic data and targeted agent experience, including real world data

• Functional and clinical validation of presumed targets and variants of uncertain significance

• Granular data on “matched therapy:” Agent, means of access, dose, toxicity and response, **including negative data**

• Ability for industry to leverage “real world data” in the development of PIP and iPSP
International legal framework for compassionate and off-label uses

Michael Vranken, ACCELERATE Platform
How do patients gain access to innovative medicines outside of clinical trials?

**Experimental drugs**
- Compassionate Use/Expanded Access
  - For single patient
  - Under direct responsibility of prescriber
  - Doctors gain medicine directly from the manufacturer

**Right to try (USA)**
- Access to certain unapproved treatments/experimental medicines (completed phase 1 trials)
- Application filed or under investigation in CT
- FDA did not determine safety or effectiveness of experimental medicine
- Possible to exclude FDA from request process

**Off-Label**
- Use of medicine used outside the terms of its marketing authorisation
- Difference in:
  - Indication
  - Dosage
  - Dosing Frequency
  - Duration of Use
  - Administration

**Approved medicines**
How do patients gain access to innovative medicines outside of clinical trials?

**Compassionate Use/Expanded Access**
- Medicine which is not fully evaluated in clinical trials
- No treatment available for Life-Threatening Illness
- Disease cannot be treated satisfactorily by authorised medicines
- Safety & efficacy profile required
- Group of patients/individual patients
- Medicine undergoing CT/Applying for MA
- Competent authority involved

**Named Patient Base**
- For single patient
- Under direct responsibility of prescriber
- Doctors gain medicine directly from the manufacturer

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# How do patients gain access to innovative medicines outside of clinical trials?

## Experimental drugs

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• Difference in:  
  • Indication  
  • Dosage  
  • Dosing Frequency  
  • Duration of Use  
  • Administration |
Compassionate use around the world

Australia
• Special Access Scheme
  • Case by case evaluation
  • 3 pathways:
    • A: Notification for UMN
    • B: Application for medicine without established history of use
    • C: Notification for established history and indication

Canada
• Special Access programme
  • Patient specific request
    • life-threatening conditions
  • Future use request
    • future medical emergency

USA
• Expanded Access Programme
• Righty to try
Compassionate use around the world: Europe

Europe
Established by Article 83 of Regulation (EC) No 726/2004, this tool is designed to:
• facilitate and improve access to compassionate use programmes;
• favour a common approach
• increase transparency between Member States.

Germany
• Compassionate Use Programme
  • NCA responsible + advising role of institute (Paul-Erlich)
• Named patient Programme

France
Temporary authorization for Use (ATU)
• Cohort ATU
  • Efficacy and safety strongly presumed
• Nominative ATU

Lithuania
No programme available

For most high income countries, a legal framework for CU exists.
Heterogeneity in frameworks
Physician perspectives on compassionate use in pediatric oncology

• Survey of 132 Paediatric oncologists in the USA

• Most common barriers for CU programme reported:
  • Inability to identify a drug that had the potential to help patients
  • Lack of knowledge, experience or understanding of the application process
  • High burden of administrative workload in the application process

Facilitation programmes for Compassionate Use

• FDA Project Facilitate
  • Helps oncologist with Expanded Access Programme request

• KidsVCancer Compassionate Use Navigator
  • Personal assistance & information on CUP
  • as a service for the pediatric oncology community – physicians, families, and advocates
Off-label medicines

• Prescribing off-label is frequent in the paediatric population*

• Europe: not regulated by EU, decision and responsibility on behalf of prescribing physician.

• USA: Not regulated by FDA and common practice, responsibility on behalf of prescribing physician

• Reimbursement issues

• Higher rates of adverse drug reactions events due to off label prescribing

Conclusions & next steps

• A legal framework for access to experimental medicines exists.
• Different and complex regulations around the world.
• Heterogeneity in regulatory instruments to access to experimental drugs in Europe

• How data is captured on safety and efficacy for both compassionate and off label uses?
• How can potentially valuable Real-World Data be available to suggest further evaluation of a drug or not?
• First step - ITCC-ACCELERATE Platform survey to determine current processes and data capturing in Europe, Canada and Australia.
Securing Access to Innovative Medicines – the SACHA Project

Pablo Berlanga
Department of Pediatric and Adolescent Oncology,
Gustave Roussy
pablo.berlanga@gustaveroussy.fr
Current access for children/adolescents with cancer to therapeutic innovation in France

- **Discussion & validation in MTB**
- **National molecular tumor board**
- **Therapeutic recommendations**
- **Phase I/II clinical trials (including ITCC trials)**
- **Clinical care**
  - **Tumor molecular profile**
  - **MAPPYACTS II trial (including liquid biopsies)**
- **Research**
  - **MAPPYACTS II trial (including liquid biopsies)**
  - **1WGS and RNAseq**

**If case of disease relapse/progression**

What about innovative anticancer therapies administered outside their marketing authorisation/clinical trials?
SACHA study: “Secured Access to innovative medicines for CHildren with cAncer”

- Developed by the New Drug Development Committee of the French Society of Pediatric Oncology (SFCE) in collaboration with the 7 interregional pediatric oncology networks (OIR) of the French National Cancer Institute (INCa)

- French observational study consisting on prospective collection of toxicity and efficacy data of off-label & compassionate administration of anticancer therapies, administrated to patients ≤ 25 years-old with pediatric tumors outside the frame of clinical trials

- Patients with recurrent/refractory malignancies to be discussed at the interregional multidisciplinary tumor boards (RCPP) of the OIRs. Data collected by a validated pharmacovigilance tool (VIGINOM)
SACHA study: “Secured Access to innovative medicines for CHildren with cAnCer”

- Study opened in March 2020 (NCT04477681)
- Currently 106 patients included
Current access for children/adolescents with cancer to therapeutic innovation in France

If case of disease relapse/progression

Clinical care
- Tumor molecular profile
  - MAPPYACTS II trial (including liquid biopsies)

Research
- WGS and RNAseq

Discussion & validation in MTB

National molecular tumor board

Therapeutic recommendations

Phase I/II clinical trials (including ITCC trials)

SACHA
Acknowledgements

• SACHA Scientific Committee: Nicolas André, Emilie de Carli, Nadège Corradini, Stéphane Ducassou, Marion Strullu, Natacha Entz-Werle, Anne Sophie Defachelles

• Pharmacovigilance Unit Gustave Roussy: Salim Laghouati, Lee Aymar Diakou Ndounga

• SFCE New Drug Development Committee

• SFCE Precision Medicine Committee: Virginie Gandemer, Dominique Valteau-Couanet, Gilles Vassal

• Funders:
Summary of problems found in evaluation

- Insufficient development in areas of greatest unmet medical needs
  - Developments do not address highest needs for children
  - ‘One-size-fits-all’ incentives and rewards <-> unmet needs
- Scientific and technological developments cannot be fully exploited
  - Exclusion from obligation to conduct PIPs (mechanism of action)
  - Innovative PIP designs
- Availability and accessibility varies across MS
  - Limited link between incentive and placing on market
  - Limited generic competition after expiry of exclusivity periods
- Certain procedures inefficient and burdensome
Objectives of the revision

• To foster research and development of medicines for paediatric diseases in areas of unmet need and in better alignment with patient needs;

• To ensure availability and timely access of patients to paediatric medicines;

• To ensure legislation to be fit to embrace technological and scientific advances;

• To provide effective and efficient procedures, for assessment and authorisation.
Impact assessment - Baseline

• The current Regulation will continue to apply.

• Non-legislative actions developed in the framework of the joint EMA - European Commission Paediatric Action Plan may allow for short term solutions for example in PIP procedures.

• SPC inefficiencies – SPC legislation revision.
Impact assessment

• Revise elements of the PIP procedure:
  ➢ When appropriate, more flexibility in data submitted in a PIP (adaptative PIP);
  ➢ Take into account the mechanism of action of products (oncology and maybe other areas) when agreeing on PIP (link with unmet needs);
  ➢ Deferrals, timely completion of PIPs.
Impact assessment

• Define in legislation how to identify which products/developments should be further supported as addressing unmet therapeutic needs of children;
• Define how to support such products/developments and when;
• Better assess the access and availability problematics in children and possible solutions (including PUMA).
EU Pharmaceutical strategy

Ensure access and affordability of medicines for patients and health systems sustainability

Ensuring access and availability addressing shortages

Enabling sustainable innovation

Succeeding on the global level
Flagships of the pharmaceutical strategy

Ensure access and affordability of medicines for patients and health systems sustainability

**Unmet needs**
- Boost **novel antibiotics** - 2021
- Restrict and optimise the use of antimicrobial medicines (2021)
- Support medicines for **children and rare diseases** (2022)
- Collaboration on unmet needs, evidence generation, HTA (2021)

**Accessibility**
- Revise the **system of incentives and obligations** in legislation to support innovation, access and the affordability of medicines (2022)
  - Improve access to **generic and biosimilar medicines** (2022)

**Affordability**
- Address in legislation the **market effects** impacting on affordability (2022)
- Develop **mutual learning and best-practice exchange** on pricing, payment and procurement policies (2021-2024)
## Flagships of the pharmaceutical strategy

### Enabling sustainable innovation

#### Fertile environment
- Optimise the **supplementary protection certificates system** (2022)
- Legislative proposal on **European Health Data Space** (2021)
- **Interoperable data access infrastructure** to facilitate secure cross-border analysis of health data (2021-2025)
- Support **public-private and public-public partnerships** (2021)

#### Innovation and digital transformation
- Adapt legislation to **cutting-edge products, scientific developments** and transformations (2022)
- **Enhance dialogue** among regulatory and other relevant authorities (2021)
- Take forward the use of **HPC and AI** (2021-2022)
- Establish the secure federated access to 10 million **genomes** (2025)

#### Flexible regulatory system
- **Simplification and streamlining** of approval procedures and flexibility for timely adaptation (2022)
- **Optimise the lifecycle management of medicines** more efficient and adapted to digitalisation (2021-2023)
Flagships of the pharmaceutical strategy

Ensuring access and availability addressing shortages

Secure the supply
- Revise the legislation to enhance security of supply and address shortages (2022)
- Launch a structured dialogue to identify vulnerabilities in the global supply chain (2021)
- Ensure increased transparency of the industry on the supply chains (2021)

High quality, safe and environmentally sustainable
- revise manufacturing and supply provisions in the legislation to ensure environmental sustainability, quality and preparedness (2022)
- revise the legislation to strengthen environmental risk assessment requirements and conditions of use (2022)

Crisis response mechanisms
- Proposal for an EU Health Emergency Response Authority (2021)
Succeeding on the global level

Work with the EMA and the network of national regulators, to promote regulatory convergence to ensure access to safe, effective high-quality and affordable medicinal products globally (ongoing)
Next steps revision of the orphan and paediatric legislation

- Impact Assessment
  - Public consultation
  - Targeted consultations
  - Interviews
- Legal Proposal(s) (Q1 2022)
Revision of the pharmaceutical legislation

• Roadmap inception impact assessment (Q1/2 2021)
• Evaluation and impact assessment
• Public consultations (Q2/3 2021)
• Other consultation activities (Q2/3 2021)
• Adoption of proposal(s) (Q4 2022)
Thank you

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The ACCELERATE Paediatric Strategy forum initiative and further development

Andy Pearson, ACCELERATE
ACCELERATE Oversight Committee

**ACCELERATE Steering Committee**

- Andy Pearson
  - Oversight Committee Chair

**Global paediatric cancer community**

- Beth Fox
  - St. Jude

- Karsten Nysom
  - Rigshospitalet

**Regulators**

- Dominik Karres
  - EMA

- Koen Norga
  - PDCO

**Patient Advocates**

- Susan Weiner
  - Children’s Cancer Cause

- Nicole Scobie
  - Zoe4Life

**Trade Associations**

- Fiona Hemming
  - EFPIA

- Anjali Sharma
  - Phrma

Essential and enormous support by Andrea Demadonna
The ACCELERATE Paediatric Strategy forum initiative and further development

- Activity during 2020
- General principles
- Future directions
The ACCELERATE Paediatric Strategy forum initiative and further development

Work plan for 2020

• Consolidate and expand ACCELERATE Paediatric Strategy Forums as they will be key in facilitating prioritization in the new environment
• Set-up impact assessment
• Set-up follow-up meetings and strategy update
• Reduce time to publication and expand dissemination outreach
Based on a mechanism of action approach selection and prioritisation of innovative drugs is required driven by science and meet patients’ unmet needs is required.

**Goal** - To share information between all stakeholders, to evaluate science, to inform paediatric drug development strategies and subsequent decisions – multi-stakeholder meeting.

- Discussion involving all stakeholders
- No regulatory decisions are made during the meeting
Pediatric Strategy Forums

1st PSF on ALK Inhibitors
30-31 Jan 2017, London
6 products; 5 companies

ALK update virtual meeting
13-14 Jan 2021
55 participants

4th PSF on AML
11-12 Apr 2019, Rotterdam
26 products; 18 companies

AML update meeting
Nov 2019
25 participants

2nd PSF on Mature B cell Malignancies
13-14 Nov 2017, London
20 products; 14 companies

5th Forum on Epigenetic modifiers
23-24 Jan 2020, Philadelphia
16 products; 12 companies

BETi update virtual meeting
10 Jul 2020
55 participants

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Manuscript European Journal of Cancer, Feb 2019

Manuscript European Journal of Cancer, Jan 2020

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Manuscript European Journal of Cancer, Jul 2020

Manuscripts European Journal of Cancer
Sep 2020/2021

3rd PSF on Checkpoint Inhibitors
5-6 Set 2018, London
20 products; 16 companies

Manuscript European Journal of Cancer
Jan 2020

6th PSF on Car-T Cells
25, 26 & 27 May 2021, Virtual

7th PSF on Sarcoma
Q4 2021, Virtual

2017-2019

2020-21 (achieved)

2021 (planned)
Paediatric Strategy Forum for Medicinal Product Development of Epigenetic Inhibitors

23 and 24 January 2020

• First - Early in development of epigenetic modifiers – relevant to RACE
• First to be held in United States – Philadelphia
• Kimberly Stegmaier and Franck Bordeaut – experts

**Objective**

• To **identify** epigenetic targets or mechanisms of action relevant to paediatric cancer
• To **define** the landscape for paediatric drug development of epigenetic modifiers in children and adolescents
Paediatric Strategy Forum for Medicinal Product Development of Epigenetic Inhibitors

Conclusions

• Menin-MLL – Evaluate role in ALL and AML – Very high priority
• Roles of DOT1L, EZH2, EDD, LSD1 and Retinoic acid receptor alpha agonist defined
• Importance of combinations
• Meeting on BET inhibitors - NUT midline tumours, MYCN amplified malignancies, fusion driven malignancies

Published 7 and half months after Forum
BET Inhibitors - Follow up meeting
10 July 2020  VIRTUAL

Context
• At least 10 pan-BET inhibitors in clinical development
• Relevant paediatric population is \textbf{not large} enough to accommodate clinical trials of all these BET inhibitors

Objective
Discuss BET inhibitors - develop a \textbf{consensus} about their development, including prioritization and their specific roles. between relevant biopharmaceutical companies and academics

Conclusions
• Further clinical development of other pan-BET inhibitors in children should await the results of the first paediatric clinical trial of BMS-986158
• Clinical need for global access to BET inhibitors for NUT carcinoma - development & regulatory pathway - children, adolescents and adults
• BDII-selective inhibitors, CNS penetrant BET inhibitors dual-targeting BET/p300 bromodomain warrant further pre-clinical investigation

\textit{European Journal of Cancer in press}
Paediatric Strategy Forum for ALK Inhibition – 2017

• Landscape has changed – 3 PIPs agreed or planned, clinical trials planned or in progress
• 78 Multi-stakeholder participants - Regulators as observers
• 5 companies - 9 medicinal products

Objectives

• With current trials planned or ongoing, what are the current unmet needs?
• *How do we evaluate and prioritise second/third generation products?
• *What lessons have we learnt?
  * Relevant to ALK inhibitors and other products and RACE

Conclusions

• ALCL - goal is to include ALK inhibitors in front-line therapy
• IMT - need for a global approach
• CNS tumours - genomic assessment & concern about very small number of patients in multiple trials
• Neuroblastoma - Evaluation in front-line studies,
• Generic issues - Real World Evidence, Companion diagnostics, Evaluation and prioritisation of second/third generation products
The ACCELERATE Paediatric Strategy forum initiative and further development

• Activity during 2020
  ➢ General principles
• Future directions
The ACCELERATE Paediatric Strategy forum initiative and further development

General principles

• Global academic collaboration
• Early academia-multi company engagement
• Early engagement with regulators
• Simultaneous submissions to FDA and EMA
• Coordinated and integrated strategy
• ‘Real world evidence' supporting development and registration efforts
• Platform trials
• Very rare malignancies with same biology in adults - development & regulatory pathway - children, adolescents and adults
General principles

Multiple products of the same class

Focused and sequential development

• Agreement by all involved (industry and academia) based on scientific arguments
  ▪ Which product, based on current evidence, is considered to have the highest potential to address unmet medical needs
  ▪ The sequence in which other available (or emerging) products should be developed or deferred. So that as soon as a development is completed (either due to futility or efficacy) others are already prepared for evaluation

• Engage regulatory agencies in a consolidated effort early in development
The ACCELERATE Paediatric Strategy forum initiative and further development

- Activity during 2020
- General principles

➢ Future directions
Evaluation of Impact of Paediatric Strategy Forums

• Initial analysis – other aspects, can and will be reviewed in the future
• **General** analysis of the Forums then **Specific metrics** relating to B-cell and Checkpoint Forums (as an adequate time has elapsed to allow their effect to be analysed).
  - Questionnaire focusing on industry
  - Questionnaire focusing on academics
    - Individual assets presented at Forum – publicly available date current status at EMA and FDA and status of clinical trials
    - Perspective of regulators and patient advocates
Evaluation of Impact Of Paediatric Strategy Forums

Specific metrics relating to B-cell and Checkpoint Forums

Data generated by EMA and FDA

• Data of the impact of the B-cell Forum - Number of Waivers – EMA, relevant data from FDA
• Data of the impact of the Checkpoint Forum – PIPs requesting monotherapy trials EMA, relevant data from FDA

Data generated by ACCELERATE

• Review of clinical trials in relation to Checkpoint Forum - Number of monotherapy trials commenced since Paediatric Strategy Forums (other than lymphoma/hypermutant tumours) and comparison to Paediatric Strategy Forums situation
Sixth Paediatric Strategy Forum for Medicinal Product Development of CAR T-cells children

25, 26 and 27 May 2021 – Virtual

Key questions

Disease specific

ALL
What are the needs of children with ALL for CAR T-cell therapy and what is the optimal timing of CAR T-cell therapy in ALL therapy, to maximize its curative potential and replace more toxic therapies?

Solid tumours
How can we access CAR T-cell therapy for children with solid tumours?

Disease agnostic
How can the access to CAR T-cell products within academic multicentre trials be secured?
How can next generation CAR T-cell products address any remaining unmet medical needs?
How can CAR T-cell therapy be accessed after a clinical trial with positive findings?

Claudia Rossig, Andre Baruchel, Crystal Mackall, Nirali Shah - Experts
Pediatric Strategy Forums

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July 2020

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Sep 2020/ 2021

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Q4 2021, Virtual

2017-2019
2020-21 (achieved)
2021 (planned)
Choosing the topic of the next Paediatric Strategy Forums - 2022

**Process**

- Survey November / December
- Review by Paediatric Strategy Oversight Committee
- Voting by attendees of ACCELERATE Conference

**2022 - Modified due to COVID**

- Spring – Face to face meeting in Europe - EMA - Topic based on voting 2020 - Discussed by Oversight Committee
- Autumn - Face to face meeting in USA – based on voting ACCELERATE Conference 2022
Patient Advocates

Key role in Summarising the Forum
Conclusions

• Attempted to adapt to the COVID situation with virtual meetings – Aim 2022
  Face to face meetings alternating Europe and USA
• Importance of clear conclusions
• Implemented follow up meetings
• Accelerated time to publication
• Evaluating the impact of the Paediatric Strategy Forums
• Working towards “Living” prioritisation
• Continually developing and adapting to needs
Thank you
International Collaboration initiative

Greg Reaman, U.S. Food and Drug Administration
Teresa de Rojas, ACCELERATE
Nicole Scobie, Zoe4Life
Rationale & Goals

Identify the real obstacles to international cooperation and collaboration

Develop principles and best practices for global clinical research in the US-EU-UK-Canada-JAPAN to enable pediatric oncology focused cooperative groups and clinical trial centers to collaborate to ACCELERATE drug development

Provide synergy, but not overlap, with other WGs (e.g. Fit-for-Filing) and ITCC Sponsor Committee

Need for intercontinental collaboration in pediatric oncology to facilitate new drug development and build robust practice changing trials with sufficient sample size to make meaningful conclusions
## Working Group Members

### Academia
- Todd Alonzo
- Andrea Biondi
- Kathy Brodeur Robb
- Maryam Fouladi
- Tom Gross
- Steve Hunger
- Geoff McCowage
- Alberto Pappo
- Martin Schrappe
- Maria Grazia Valsecchi
- Brenda Weigel
- Peter Wejbora
- Jim Whitlock

### Advocacy
- Leona Knox
- Nicole Scobie
- Vicki Beugner
- Donna Ludwinski

### Industry
- Darshan Wariabharaj
- Elly Barry
- Anjali Sharma
- Kathleen Neville

### Regulators
- Dominik Karres
- Gregory Reaman

### Core Group
- Gregory Reaman
- Teresa de Rojas
- Nicole Scobie
- Leona Knox
- Darshan Wariabharaj
- Andy Pearson
- Gilles Vassal

### ITCC Sponsorship
- Pamela Kearns
- Michel Zwaan
**Work Packages**

**WP-1.** Systematic review of international clinical trials  
Landscape analysis

**WP-2.** Data survey of intercontinental trials  
Identify obstacles

**WP-3.** Multi-stakeholder discussion and consensus  
Find solutions
Conclusions

Only a small proportion of pediatric cancer trials have been conducted intercontinentally over the last decade. Most of them (2/3) were industry-sponsored.

The number of intercontinental trials was stable over time, with a worrisome decreasing trend for academic trials.

The majority of industry early phase (90%) and phase 2 (95%) trials involved North-America and Europe, with less involvement of Oceania or Asia (<50% in both types of trials).

Only 25% were late phase trials – most of those with a pediatric focus were carried out by academic sponsors, predominantly COG trials (US-Oceania collaboration).

The next steps of our WG will identify existing hurdles and propose solutions to improve intercontinental collaboration in clinical research for the benefit of children and adolescents with cancer.
Thank you!
Long-Term Follow-Up Working Group

Mark W. Kieran, MD, PhD Senior Director, Pediatric Oncology, BMS
Danielle Horton Taylor, MSc, MPhil Parent Representative, ACCELERATE
1. Our vision and goals
2. Submission of our first manuscript to Pediatric Blood & Cancer (under review)
3. The LTFU model
4. Progress of the 4 sub-working groups
5. Plans going forward → pilot trial
Vision and Goals

Create an international, open and harmonised data registry to collect existing data of long-term health outcomes in children treated with new anti-cancer agents to enable **safe and correct use of new cancer drugs**

1. Fulfill the regulatory requirements of the marketing authorization holders

2. Can be used to increase knowledge of the long-term safety and follow-up care of new modalities to support the best use of these therapies
A global approach to long-term follow-up of targeted and immune based therapy in childhood and adolescence

Mark W. Kieran1,2,19, Hubert Caron3, Jeanette Falck Winther4,18, Tara O. Henderson5, Riccardo Haupt6,18, Lars Hjorth7,18, Melissa M. Hudson8, Leontien Kremer9,18, Helena J. van der Pal10,18, Andrew D.J. Pearson11; Leonardo Pereira12; Gregory Reaman13, Roderick Skinner14,18, Gilles Vassal15, Susan Weiner16 and Danielle Horton Taylor1,17,19 for the ACCELERATE Long-Term Follow-Up Working Group
Model

- A global registry
- Separate informed consent
- Data collection for selected new agents
  - Includes core LTFU data as well as modular data (based on drug or pathway)
- Central standardised database
  - data collected and entered by treating physicians with reimbursement for time and effort
  - data reports to pharma customers as fee for service
  - Opportunity for use by academia for independent research
- Legal entity needed: ‘Accelerate LTFU Registry’

Core activities: infrastructure / contracting / data collection+reporting / finance
LTFU Model

1. ACCELERATE LTFU Legal Entity
   - Treating physician
   - Patient / Caregiver
   - Pharma customer
   - Academia customer

2. Data Commons Group
   - Informed Consent
   - New drug

3. Standard data collection system
   - Data sets (Core + Modular)
   - Data transformation
   - Data harmonisation
   - Data verification
   - Data cleaning

4. ACCELERATE Steering Cie

5. Aggregate Data extraction, transformation and analysis
Pediatric Data Commons platform

- Standardised data definitions (harmonisation)
- Already collecting and storing data from Europe, North America, Asia
- Designed to meet local regulatory requirements
- Fee for service infrastructure
- Can leave and take our data with us

Next Steps
PanCare LTFU program existing infrastructure for collection of data in Europe

- How to transfer to Pediatric Data Commons to avoid duplication of effort
- Many contracting issues to work out
“ACCELERATE Long Term Follow up Registry”

- There will be an appraisal of different options to identify the best model for the ‘legal entity’ to house the registry. This will be separate from ACCELERATE legal entity
- This legal entity will be responsible for finances, staffing, contracting
- Governing board of NGO will include
  - At least one member of ACCELERATE Steering Committee
  - Other necessary expertise for oversight, e.g., business, legal, stakeholder representation

Next Steps
Governance needs budget to create NGO
Use of policy and procedures from existing NGOs to guide LFTU NGO
Assessment of LTFU data elements from multiple groups

- Development of a consensus on necessary data elements for general LTFU
- Drug or pathway specific modules to expand data in areas of need related to specific drugs

**Next steps**

- Need for standardisation of dictionary terms in Pediatric data Commons Data
- Discussion of data elements with EMA and FDA
- Consensus meeting for Data Elements (Spring 2021)
Support from pharma on concept of LTFU Registry

Next Steps

- Development of a formal governance structure
- Included as a separate legal entity (see Governance) since financial support is included
- Development of a pilot assessment of the Registry, based on three drugs from three different companies
Acknowledgments


• **Accelerate Leadership:** Andy Pearson, Gilles Vassal

• **Accelerate Support and Coordination:** Andrea Demadonna, Teresa de Rojas, Michael Vranken
Fit for Filing Working Group

Pam Kearns, SIOPE & University of Birmingham
Elly Barry, Pfizer, Inc.
Overview of Working Group

**Objective:**
- develop best principles on how the design and deliver a trial with a dataset that can be included in a package for filing

**Kicked off in 2019**

**Multi-stakeholder representation**

**Academia:**
- Pam Kearns (University of Birmingham)
- Bram De Wilde (Ghent University Hospital)
- Beth Fox (St. Jude Children’s Research Hospital)

**Regulatory:**
- Greg Reaman (FDA)
- Dominik Karres (EMA)

**Industry:**
- Elly Barry (Pfizer)
- John Manlay (Pfizer)
- Mark Kieran (BMS)

**Patient Advocacy:**
- Carol Ludwinski

**Additionally:**
- Rosanna Ricafort (BMS)
- Kathleen Neville (JNJ)
- Marieke Willemse (Princess Maxima)
Summary of Work Plan

• 2019
  • Survey of industry and academic experiences
    • Successes, challenges, lessons learned
  • Identified 4 concentration areas:
    • Essential Documents
    • Essential Data
    • Data Management
    • Resources

• 2020
  • Deeper dive to better understand the issues and develop aligned recommendations/principles
**Survey of Industry Sponsors**

- Most companies are/will be involved in these types of collaborations
  - Work to be done in alignment between protocol and regulatory obligations/expectations
- Data collection - incomplete
- Data monitoring/cleaning – not comprehensive
- Database/data format issues
- Incomplete documentation
- CSR: Usually Industry-generated
- Funding model
  - You get what you pay for

**Survey of Academic Sponsors**

- Academic sponsors have well prepared systems to conduct trials (multi-centre, multi-country) compliant with GCP and associated regulations
- The QMS and SOPs are not written specifically to comply with ICH E6
- Not possible to assess in survey whether of not their current SOPs would generate data that could be readily submitted as part of a filing package
- End of study reports standard but not experienced in writing E3 CSR (usually outsourced)
1. **Essential Documents** (Elly and Dominik)
   - Build from ICH guidelines re: trial documentation
   - Identify additional documents required for filing, with rationale

2. **CRF Essential Data** (Rosanna, Beth and Greg)
   - Look at standardized CRFs from Industry and Academia
   - Identify common data elements and differences

3. **Data Management** (Pam, Bram, Elly and John)
   - Learn from industry DM standards → recommendations/guidance for academic sponsors

4. **Operational/Resources** (Kathleen, Pam, Donna, Greg, Marieke)
   - Gather data from academic sponsors and industry re: cost of resourcing for « Fit for Filing » trials

**Four Sub-teams**
Current Landscape

Adult

Paediatric

Funding source

- Industry
- Industry|Academia
- Government
- Academia
- Academia|Government
1. Early planning is essential
   • Early communication amongst academic research consortia, pharmaceutical industry and regulators

2. Prospective collaboration and agreements
   • Careful planning, with realistic expectations of all parties will avoid failure to meet both clinical as well as commercial endpoints.

3. Alignment of data collected to meet study objectives and regulatory commitments
   • Our review highlighted that whilst there are disparities between data normally collected for an academic-sponsored trial and those needed for a submission to be fit for filing, it is not an insurmountable hurdle if planned from the start.
   • It is much more challenging to retrofit already collected datasets to meet ICH-GCP E6 compliance

4. Recognition of shared responsibilities

Recommendations: General Principles
Recommendations: Essential Documents

Development of an essential document checklist to serve as a template for pediatric oncology clinical trials

1. Follow ICH E6 which outlines the essential documents that a study sponsor should collect and maintain before, during, and following the conduct of a study
   • Protocol versions, contracts, IRB documentation, ICDs, monitoring reports, CRFs, etc.

2. Additional documents/documentation beyond ICH E6 may be required by regulatory agencies
   • SAP, DM plan, EDMC charter/minutes, financial disclosures

3. Alignment on which party is responsible for which documents and where they are filed
1. Development of a paediatric oncology specific essential data list to serve as a template for paediatric oncology clinical trials
   • balance between ensuring all data that are critical to a filing package are included but without collation of unnecessary data not required to answer the trial question nor mandated by the regulators

2. The level of detail by which patient data is captured should be scrutinized to be relevant for the safety evaluation of the investigational product of trial
   • For example, previous and concomitant medications should not necessarily be collected with the same level of detail. This should clearly be stated in the trial protocol.

**Recommendations: Essential Data**

*All essential patient related data required to meet the trial end points plus those mandated by Regulators for filing*
Recommendations: Data Management

“quality factors are considered to be critical because, if their integrity were to be undermined by errors of design or conduct, the reliability or ethics of decision-making would also be undermined.”

*(ICH E8(R1)*

1. **Data Management Plans**
   - the additional requirements, over and above the standard non-commercial QMS must be established from the start of a study
   - a close partnership between the academic sponsor and industry in co-developing the case report forms (CRF) and the data collection strategy

2. **Trial Databases**
   - availability of a validated database system that complies with ICH E6 R2 and is 21CFR11 compliant

3. **Pre-agreement of Data Management Procedures**
   - data query procedures, data monitoring plans, audits
   - data transfer agreement should be in place before trial is initiated and should define the number of data transfers (test, prior to deliverables, at deliverable)
Recommendations: Resources

‘You get what you pay for’

1. **Industry Transparency**
   - Full disclosure on the anticipated use of the data at the outset, as this has a significant impact on the conduct of the study
   - Full disclosure on envelope of industry funding available

2. **Academic Transparency**
   - Opportunity for academic sponsors to share their experiences, particularly with respect to vendor costs for databases, drug distributors and monitoring services

3. **Recognition of the mutual benefit**
   - The collaboration is beyond costs and profits but patient benefit is at the core of the endeavor
2021 Work Plan

• Developing a Manuscript: Submit 1H 2021

• Develop education program to support investigators and academic sponsors understand the needs for ‘fit for filing’ trials
  • Insights from FAIR Trials WG?
Acknowledgments and Thanks

Carole Lecinse
  COG
  St. Jude
  NANT
  POETIC
Beat Childhood Cancer Consortium
CRCTU University of Birmingham
Princess Maxima Centre, Utrecht
Gustav Roussy
  Amgen
  Abbvie
  Novartis
  Roche
  Gritstone
  BMS
  Lilly
The Fostering Age Inclusive Research (FAIR) Trials project

Nathalie Gaspar, Institut Gustave Roussy
Chris Copland, University of York
FAIR Trials Working Group

https://www.accelerate-platform.org/fair-trials/

Fostering Age Inclusive Research

- Associated members
  - National authorities
  - Regulatory representatives
  - Ethics Committees
  - Academics from the main European countries

Core group

- Academic drug development
  - Pediatric oncologists

Pharma
  - Roche Genentech
  - BMS
  - Novartis

Patient/parent representatives
  - AYA

- Raise Awareness
- Gain Endorsement
- Identify Successful Trials
- Develop Tools for Colleagues and Supporters
The First three STAMPS
- Roche: TAPISTRY (Phase II)
- Eli Lilly/Loxo Oncology: LIBRETTO-001 (Phase I –II)
- Eli Lilly and Cie: LIBRETTO-531 (Phase III)
ESMO/SIOPE AYA Educational 2020

https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/translational-research-is-cancer-in-aya-different
Patient/parent support

Links developed with Patients and Survivors

- Why FAIR trials?
- Multistakeholder supports to FAIR Trial Initiative
- Paediatric and Medical Oncologists
- Patient and Parent advocates
- Industry
- Regulatory

Mariana Coutinho, Portugal

“Personally, I have witnessed how devastating it can be for a teenager to receive the news that they can't be helped because they don't meet an age inclusion criteria. A friend of mine, who was diagnosed with rhabdomyosarcoma and was just a few months away from being 18 years old, was denied access to a clinical trial because of his age. I am thrilled to be part of this initiative as a patient advocate and I wish to help shape the dialogue and raise awareness on this very important issue, hoping to encourage the different stakeholders to recognise how not only patients but also the medical and research community can benefit from this more inclusive approach.”
Industry support

https://www.accelerate-platform.org/fair-trials/

Industry organisation letter of support

June 19, 2020

Dear Professor Vassal, Dr. Gaspar, and Mr. Copland,

The Biotechnology Innovation Organization (BIO), European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), European Federation of Pharmaceutical Industries and Associations (EFPIA), Eurepharma – the European Association of Bioindustries, and Accelerate – the Innovative Therapies for Children with Cancer in Europe (ITCe) President, Dr. Nathalie Gaspar, ACCELERATE Fostering Age Inclusive Research (FAIR) Working Group Co-Chair, and Chris Copland, ACCELERATE Fostering Age Inclusive Research (FAIR) Working Group Co-Chair,

We are writing to express our full support for the FAIR Initiative and to highlight the critical importance of including adolescents in clinical trials.

We appreciate the efforts led by the FAIR Initiative and hope to continue to partner with ACCELERATE to speed up the delivery of innovative therapies to children and adolescents.

Sincerely,

[Signatures]

E. Carter Gehani, Ph.D.
Senior Vice President, Science and Regulatory Affairs
EUCOPE

C. W. Z.

Many Chithis

E. Carter Gehani, Ph.D.
Senior Vice President, Science and Regulatory Affairs
EUCOPE

C. W. Z.

Many Chithis

Chief Medical Officer and Executive Vice President, Science and Regulatory Affairs
EFPIA

[Logos: BIO, EUCOPE, EFPIA, Accelerate]
Regulatory supports

https://www.accelerate-platform.org/fair-trials/

- Why FAIR trials?
- Multistakeholder supports to FAIR Trial Initiative
- Paediatric and Medical Oncologists
- Patient and Parent advocates
- Industry
- Regulatory

FDA guidance

EMA letter of support

EFGCP letter of support

2021 EMA Practical Guidance for industry

2021 EFGCP Practical Guidance
ACCELERATE FAIR TRIAL GROUP

https://www.accelerate-platform.org/fair-trials/

- Why FAIR trials?
- Multistakeholder supports to FAIR Trial Initiative
- Paediatric and Medical Oncologists
- Patient and Parent advocates
- Industry
- Regulatory

Interactive map

Find resources in your country!

National initiatives through ITCC contacts
Contact with paediatric oncologists involved in early drug development and AYA friendly

Paediatric and Medical Oncologists

Foster the Inclusion of Research (FAIR) Trials for Adolescents

Paediatric and medical oncologists in Europe are transforming the ACCELERATE FAIR Trials initiative into a country-by-country action plan. They are working together to break the 18 years delay, despite the fact that countries have different healthcare structures, drug development programmes and approaches to AYA population care. Here are a few sentences about each country on what is being done and why it is important. Contact details are given, should you wish to promote the initiative.

ACCELERATE FAIR Initiative – country by country Action Plan

2020-21 Update of the website ongoing
Summary paper of the changes, remaining hurdles and possible solutions
Remaining problems

• Efficient recruitment in adolescents in joint adolescent/adult trials
  • Understand the problems
  • Find solutions

• Recruitment of young adults with pediatric diseases in pediatric trials: how to avoid upper age limit?
What are your views?

What are the hurdles to including adolescents in joint adolescent/adult trials?

A. Limited incidence of the condition in the 12-17 age range
B. Competition for the same patients population (12-17 years of age) from another clinical trial
C. Absence of a pediatric sub-investigator
D. The study protocol was approved in certain institutions/countries only for 18 years old and above
E. No appropriate referral network in place to enable enrollment of adolescents
F. Absence of a pediatric ward or AYA (adolescents young adults) ward/center open for accrual
G. Operational reasons (which one?)
What are your views?

What are the hurdles to including adolescents in joint adolescent/adult trials?
FAIR Group Action Points

Objectives 2021/2022

To engage with:

• EMA
  on clearer guidelines

• Ethics committees and EUREC
  on support and collaboration

• Medical oncologists
  on support and collaboration

• Patients, parents and survivors
  through networks like YCE and establish a toolkit for action
Thanks to the active members
Thanks to ALL of you

ACCELERATE FAIR trial group

Academic drug development
Pediatric oncologists
Nathalie GASPAR, France
Lynley MARSHALL, UK
Amos BURKE, UK

Core group

Pharma
Gianluca ROSSATO, Roche Genentech
Mark KIERAN, BMS
Christina BUCCI RETCHWEG, Novartis

Patient/parent representatives
AYA
Chris COPLAND, UK
Max WILLIAMSON, UK
Mariana COUTINHO, Portugal
Evgenia MENGOU, UK

Carole Lecinse, ITCC
SIOPE/ACCELERATE team

Jump !!!
Real World Evidence

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Introduction – Setting the Scene & Definitions

• In the medical context, **Real World Evidence (RWE)** refers to evidence obtained from **Real World Data (RWD)**—data collected outside of the context of 'traditional' randomised controlled clinical trials and generated via the lived experience of real patients, in clinical practice, in real healthcare settings.

• It may potentially be derived from multiple and various sources including:
  • patient healthcare records,
  • patient registries (including disease-based registries or molecular tumour profiling registries/platforms)
  • managed access programme data
  • post-marketing approval data
  • public health registries
  • other sources (eg health insurance claims etc)

• It is observational data which may have been retrospectively or prospectively collected.
Framework for FDA's Real World Evidence Programme

• Introduction
• Definitions of Real-World Data and Real-World Evidence
• Scope of RWE Program Under 21st Century Cures Act, 2016 - 'designed to accelerate medical product development and bring new innovations and advances faster and more efficiently to the patients who need them.'
• Current Use of RWD for Evidence Generation
• Generating Evidence Regarding Safety and Effectiveness
• Supporting FDA's Regulatory Decisions of Effectiveness
• Trial Designs Using RWD to Generate Evidence
• Framework for Evaluating RWD/RWE for Use in Regulatory Decisions
• Using Trials or Studies with RWD/RWE for Effectiveness Decisions
• Assessing Fitness of RWD for Use in Regulatory Decisions
• Potential for Study Designs Using RWD to Support Effectiveness
• Regulatory Considerations for Study Designs Using RWD
• Data Standards — Appropriate Data Standards for Integration and Submission to FDA
• Stakeholder engagement

December 2018
European Medicine Agency: Real World Evidence & Big Data focus

EMA Workshop (29 November 2019)¹

- Investigate feasibility of using disease registries for cancer therapies based on genetic and molecular features.
- Registries: “organized systems that use observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure”
  1. Core data elements: minimum data elements that should be collected in cancer registries to support regulatory assessment of long term safety² and effectiveness of new cancer treatments; the feasibility of collecting the core data elements;
  2. Quality assurance: measures necessary to ensure registry data are of suitable quality to support regulatory assessments and to permit registries interoperability; conduct of data analysis;
  3. Governance: practical considerations for accessing/sharing data to be used for regulatory purposes; clarify roles of all involved stakeholders.

² Focus of ACCELERATE Long-Term Follow-Up Working Group

Real world evidence (RWE) – an introduction; how is it relevant for the medicines regulatory system?

London, EMA, April 2018

Clinical Pharmacology & Therapeutics

Review | Open Access

Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth

Hans-Georg Eichler, Francesco Pignatti, Brigitte Schwarzer-Daum, Ana Hidalgo-Simon, Irmgard Eichler, Peter Arlett, Anthony Humphreys, Spiros Vamvakas, Nikolai Brun, Guido Rasi

First published: 16 October 2020 | https://doi.org/10.1002/cpt.2083
Exploring Real World Evidence in Paediatric/AYA Oncology

ACCELERATE 2020 Breakout Session:
Beyond Randomized Trials: ‘non-conventional’ data sources for regulatory decision-making

Chairs:
• Dominik Karres (EMA)
• Lynley Marshall (Royal Marsden Hospital/Institute of Cancer Research, UK)

Co-Chairs:
• Darshan Wariabharaj (Janssen)
• Max Williamson (Member FAIR Trials Working Group)
Real World Evidence in Paediatric/AYA Oncology: Context

• Modern and constantly **changing landscape of cancer drug development** – high need to maximise the use of RWE for patient benefit

• Increasingly more **molecularly defined target subpopulations** in many if not most diseases, creating ever more rare patient subgroups to try and study in adequately powered and feasible clinical trials, within meaningful timeframes.

• **The nature of new therapies is changing**, with a general shift from chemotherapy and chemical agents to molecularly targeted treatments, immunotherapies and advanced therapies such as cellular therapies. The mechanisms of assessing the impact of these new therapies for patients need to evolve and be fit for purpose.

• It is crucial that the **safety, efficacy, clinical benefit and subsequently cost effectiveness** of the most promising new agents can be robustly and efficiently assessed in the appropriate populations, so that there is confidence in those that do pass the necessary thresholds.

• These issues particularly relevant in the paediatric and AYA oncology space, where already rare cancers with even more rare molecular sub-populations/molecular targets and sometimes multiple pharmacological agents in class challenge the feasibility of randomised control trials in some circumstances and mean that clinical development of new drugs requires global multi-stakeholder efforts to accelerate progress.
Paediatric & AYA Oncology: Community Assets

• National/International molecular tumour profiling programmes/platforms and their data bases:
  • European initiatives (MAPPYACTS, INFORM, SM-Paeds, iTHER) deliberately set up to be able to harmonise/directly compare data, eg incidence of different molecular aberrations in various cancers, ages etc, at diagnosis, at relapse, actionability etc
  • Is harmonisation with North American, Australia/NZ initiatives for greater numbers/confidence possible?
• Preclinical disease models for *in vitro* and *in vivo* hypothesis generation, target validation, proof of concept work, preclinical drug testing, eg ITCC P4, IMI2, PPTP programmes
• Pharma Managed Access Programmes, Academic access programmes eg SACHA (France), Single patient protocol registry data (Canada and others)
Paediatric & AYA Oncology: Community Assets


- Disease-based Registries, variably annotated with clinical, imaging, molecular, treatment and outcome data (eg DIPG Registry, US & SIOPE DIPG Registry – US, EU, UK, Australia, Canada).

- Genetics registries eg International BMMRD Registry (Toronto-led) & Care for CMMRD European Consortium – clinically and molecularly annotated patient data base, frequency of various aberrations, intervention and response data, international contributions.

- Rare Tumour Registries: eg SIOPE PARTNER Project (Rare tumours); SIOPE European Reference Network PaedCan; Texas Children’s (medical records, tumour and constitutional DNA – angiosarcoma, BCOR sarcoma, HCC, IMT, neuro-endocrine tumours, salivary gland tumours, thyroid cancers, undifferentiated sarcoma of liver; DFCI – NUT carcinoma; Children’s Hospital Minnesota: PPB & other DICER tumours.

- Late Effects/Long term follow-up data registries – eg for novel drugs (BRAF/MEK, Immune checkpoint inhibitors); Pancare Follow Up.
Potential Uses of RWE in Paediatric/AYA Oncology

• Informing feasibility and design of trials by robustly demonstrating real incidence of given molecular aberrations & thus patient availability for clinical trials at various points in disease journey (frontline, 1\textsuperscript{st}/2\textsuperscript{nd} relapse, beyond...) – eg ACCELERATE Paediatric Strategy Forums (ALK, B cell malignancies, AML...)

• Informing trial design: randomised control trials may remain the gold standard where possible where possible, but scope for other efficient and pragmatic designs - adaptive designs, Bayesian approaches, early stop/go designs (eg Phase I + expansions; early safety and activity signals; matched external/synthetic controls for single arm trials (as contemporaneous as possible);

• Helping to prioritise best in class compounds; facilitating regulatory applications (iPSPs, PIPs – possibility of including RWE in PIP opinions)

• Allowing iterative process of drug development/life cycle approach with milestone time points and possibility of earlier / conditional approvals to provide access where high unmet need + post marketing data collection (eg Larotrectinib approved on basis of pooled data from 3 single arm trials; Entrectinib)

• Collection of data on adolescents in adult trials (FAIR Trials project)

• Very rare populations - extrapolation where necessary/possible
Potential Challenges of RWE in Paediatric/AYA Oncology

• Data completeness (minimal data sets needed), quality, age and relevance over time.

• Issue of true equipoise between historical standard of care treatment and novel highly targeted drugs (eg NTRK inhibitor example, in diseases where traditional chemotherapy has low or at best moderate activity with significant toxicity in young patients and a well-tolerated drug with large activity effect)

• Patient consent for use of data from registries etc – important to design these well and ensure this upfront; be clear on potential future uses; parents consent for minors but what happens at age of majority?

• Single arm trials – but ORR & DOR are robust if drug effect is significant

• Patient reported outcomes are increasingly important; functional outcomes as endpoints in trials – validating tools for standardised collection etc particularly for young children

• Regulatory/HTA/Payor acceptance of evidence? EMA Big Data Taskforce – increasingly willing to explore – conversations early in development would be helpful.

• Rules/criteria to be met to allow RWE use in various situations eg disease target with very low incidence, clear molecular target, no satisfactory treatment – single arms trials with matched controls allowed, etc?
Real World Evidence Fit for Regulatory Purposes: Considerations

**Regulatory Context**
What specific decision is FDA considering?
- New indication
- Labeling revision
- Safety revision
- Benefit-risk profile

**Clinical Context**
Can the clinical question be reliably addressed with RWE?
- Prevalence of the disease
- Clinical equipoise
- Expected treatment effect size
- Relevant prior evidence

**Data Considerations**
Is the real-world dataset fit for regulatory purpose?
1. Is the data relevant?
   - Representative of the population of interest
   - Contains key variables and covariates
2. Is the data of adequate quality?
   - Minimal missing data
   - Data reliability and validity is satisfactory for study purpose
   - Known provenance and transparency of data processing

**Methods Considerations**
Are the methodological approaches of sufficient rigor?
1. Are the methods credible?
   - Appropriate analytic approach
2. Can the approach produce actionable evidence?
   - Interplay of body of clinical evidence and tolerance for uncertainty

**Fit-for-purpose RWE**

DUKE Margolis Centre for Health Policy, White Paper 2018
RWE in Paediatric/AYA Oncology: ACCELERATE Project

- **Working Group:** Dominik Karres, Lynley Marshall, Darshan Wariabharaj, Max Williamson and Mark Kieran

- **2 Phase Project** ongoing:
  - **Phase 1** - White Paper
    - Challenges and obstacles, perceived and real, associated with using RWE/registry data in support of regulatory and reimbursement processes for paediatric & AYA cancer drug development
    - Concrete examples of existing data registries which could generate RWE to be used in regulatory decision-making.
    - Examples of use of RWE where a randomised clinical trial is not feasible; where RWE could be used eg as the matched control group.
    - Key elements of data quality needed for RWE.
    - Indicate when RWE is appropriate and when it is not.
  - **Phase 2** - “Proof of concept” pilot – “Volunteers“?
    - Examples of registries and other databases to be considered for the White Paper
    - Current examples of drug development / access programmes where randomized control trials are not possible eg due to rarity – pooled data approaches, other

Please contact Andrea Demadonna at ACCELERATE who will link you to the Working Group
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