Innovative Trial Designs: Engaging with regulators, ethic committees and patients

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Agenda

1. Introduction

2. During clinical development, engaging with:
   - Regulators
   - Ethic committees
   - Patients

3. During the review of a marketing authorisation dossier
   - Continue to engage with regulators

4. Working with complex data such as Modeling & Simulation
   - Regulatory case study
During clinical development ...

• Why is important to engage with regulators, ethic committees and patients for these trials?
Developing new treatments has become increasingly challenging, complex, risky, and expensive.
Master protocols

- Overarching protocols designed to answer multiple questions, more efficiently

- Allow to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structures.

- These structures include three distinct entities:
  - basket,
  - umbrella,
  - and platform trials
Basket trial

- To study a single therapy in the context of multiple diseases or disease subtypes

The different diseases share a common characteristic (biomarkers, genetic signature, mutation, alteration... or any other feature) targeted by the investigational drug.

Leave the study
Umbrella trial

- To study multiple therapies in the context of a single disease

Patients with the same conventionally defined disease are stratified under different disease subcategories upon screening for the presence of a biomarker or other characteristic matching the investigational drug.

- Leave the study
- Studied in a ‘non-matched’ group
Platform trial

- To study multiple therapies in the context of a single disease, in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm.

![Diagram showing the process of therapy entry and exit in a platform trial.](image-url)
Advantages and disadvantages

Efficiently study **multiple compounds / multiple targets** in one operational set-up

**Identify promising or ineffective medicine earlier**, reduction of failure rate in Ph III and reduction of patient exposure to ineffective drug

Flexible design to **adapt to data being collected** and change in treatment landscape

Operational and resource **efficiency** (common control arm, infrastructures, shorter start-up time for new sites...)

**Central molecular screening**: faster accrual and increased likelihood of patient eligibility for at least one of the cohorts

**Accelerated** drug development and approval

Increased and **earlier patient access** to targeted therapies

Logistic demands: **increased complexity**, need for intensive planning, coordination, communication and transparency between all stakeholders

**Statistical challenges** to ensure data integrity and robustness

**Enforce rigorous design**

**Risk to over-estimate effects** in very small patient populations

**Regulatory reluctance** in confirmatory setting

Further hurdles foreseen with upcoming Clinical Trial Regulation (short review timelines, inability to submit parallel amendments or to link different sub-trials to a master protocol)
Stakeholders’ perspective

Regulators, Ethic Committees and Patients
What is at stake?

Communication

- Operations
  - Operational challenges
  - Trial quality and integrity
  - Oversight → sponsor/investigator/safety

- Benefit/Risk
  - Scientific integrity
  - Patient safety
  - Data transparency

Sponsor

Investigator sites / RECs

REC: Research Ethic Committees
Intense global regulatory activity

Enactment of the '21st Century Cures' Act (FDA)
- Investment in precision medicine
- FDA pilot program to promote use of innovative designs
- Upcoming guidance on complex innovative designs

EMA workshop on site and histology - independent indications in oncology

FDA workshop Promoting the use of complex innovative designs in clinical trials

DIA meeting on innovative clinical trials

CTFG f/u meeting on innovative clinical trial designs

CTFG guidance on innovative clinical trial designs


Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both
J. Woodcock (FDA) & L.M. LaVange, N Eng J Med

BfArM/PEI & ECs workshop on "Complex study designs – umbrella, basket and other complex study principles"

The evolution of clinical trials: Can we address the challenges of the future? H.G. Etchler & F. Sweeney (EMA), Clinical Trials

CTFG workshop on complex clinical trial designs

FDA guidance on master protocols and adaptive designs

Europe DIA meeting on innovative clinical trial designs
US Regulators perspective on master protocols

- Janet Woodcock and Lisa LaVange started in 2017 the discussion on master protocols (MP)
- Sept 2018, FDA modernizes clinical trial designs and approaches for drug development, proposing new guidance on the use of adaptive designs and master protocols
- Nov 2018, DIA organised a Master Protocol Workshop in the US
Engaging with regulators

- While EU health Authorities express more resistance to these designs than FDA, latest discussions and CTFG/EMA workshops show an interest in Europe to catch up

- Familiarize all involved stakeholders with MP – patients, regulators, ECs, Health Technology Assessment bodies → cornerstone to foster the conduct of such trials in the EU

- Trade associations play a crucial role in engaging with regulators to show case that master protocols can bring value to clinical research and are especially important when targeting rare or complex diseases e.g. small populations or multifactorial conditions
  - Attending workshops, participating in conferences is important to brain storm on mutually acceptable solutions

CTFG: Clinical Trial Facilitation Group
Embracing complexity isn’t easy

**Complex features**
- Many IMP profiles
- Many sites
- Many populations
- Sub-protocols
- Design adaptations

**Increased complexity**
- Complex protocols
- Different in-/exclusion criteria in sub-protocols
- Different visits and procedures in sub-protocols
- Different End of Trials in sub-protocols
- Challenges definition of clinical trial

IMP: investigational medicinal product
Research Ethic Committees in EU

- Usually established by a government or an institutional authority (such as a hospital, research institution or university)
  - must be independent from sponsors, funders, investigators, and from undue influence (e.g. political, institutional, professional or commercial)
  - typically composed of members who have qualifications and experience to review of ethical, scientific, medical, and financial aspects of a trial
  - In many countries, non-scientific members are required

- RECs can adopt a proportionate approach to ethics evaluation: the greater the burden of research, the greater the scrutiny!

- Most RECs are overloaded with administrative tasks and have not enough capacity to focus on their key obligations
Ethic Committees’ perspective on Master Protocols

- RECs must examine and evaluate whether a research project is justifiable and reasonable
  - Medically
  - Scientifically
  - Legally

- Most of RECs meet only bi-monthly with limited review time for each trial

- Lack of review time for protocol, IB and insurance/ compensation/ indemnity agreements

- Lack of knowledge, expertise in innovative complex designs and in general with more complex matters such as biomarkers, advanced therapies etc.
  - CTs are often randomly assigned to RECs rather than according their specific expertise (e.g. Oncology, paediatrics)

- Complex innovative clinical trial designs are a significant burden for RECs
What sponsors can do to help

- **4Cs Protocols**
  - Clarity
  - Coherence
  - Consistency
  - Concision

- **Visual outline of the master protocol and its sub-protocol(s)**
  - Outline clearly the objectives of the clinical trial
    - Scientific value
    - Patient’s safety and burden

- **Overarching view of the indemnification scheme**

- **User friendly Informed Consent Forms (ICF)**
  - Consider using new tools such as electronic informed consent forms, especially if the trial is complex
Patient’s perspective in RCTs

- Screening burden for biomarker trials
  - Many patients screened for each patient recruited
  - The solution would be having one screening platform

- Patients struggle to find the optimum trial; even if in a clinical trial, enrolled in suboptimal arm

- Multitude of individual, sequential trials, competing trials make patient recruitment difficult
  - identify and target therapies to subpopulations, or for rare diseases

- Screening burdensome = collect, transport, test
- Expensive = some tests are $$$
- Disappointing = no trial for most patients
What master protocols can offer to patients

- Patient-centric approach by screening patients just once and enrolling them in an optimum treatment arm
- Timely access to multiple targeted therapy trials, with an increased chance of being enrolled in an active treatment arm
- Enable patient advocacy groups to expedite access to new clinical trials and treatments for the patients they represent
What sponsors can do to help

- Including the patient’s perspective in designing the MP trial
  - E.g. via patient associations

- Communicate with patients on the aim and features of the trial by having legible informed consent documents or even electronic tools
  - Visual outline of the trial and sub-protocols
  - Eventually prepare educational material

- Communicate after the end of trial in thanking participating patients and preparing a lay summary of the trial results

- Involve patients’ association in future trials regardless of the outcome of previous trials
Continue to engage with regulators...

...during marketing authorisation review
New drug development paradigm

Phase I
Hypothesis generation
Basket trial/Platform trial

Phase II
Hypothesis testing
Enrichment trials
Umbrella trial
Platform trial

Phase III
Confirmation/Phase IV
Post-approval
RCT, RWE pragmatic trial

PRIME, breakthrough designation
Conditional approval/marketing authorisation
Accelerated Review, Accelerated Approval

RCT: Randomized Clinical Trials
RWE: Real World Evidence
MA: Marketing Authorisation
PRIME: Priority Medicine Scheme

EU Regulatory Development and Policy
Master protocols introducing R&D paradigm swift?

- Traditional therapeutic label
  - First-line monotherapy of metastatic colorectal cancer
- Randomised controlled trial (RCT) in patients with metastatic colorectal cancer
  - 8-10 yrs
- Histology-independent label
  - Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours
- Basket trial in patients with biomarker-positive solid tumours
  - ~4 yrs
Potential of basket trials: Towards histology-independent indications?
Keytruda® (pembrolizumab) – MSI-H approval

- Trial started with colorectal cancer but soon addition of:
  - gastric cancer,
  - pancreatic cancers,
  - brain tumours,
  - prostate cancers
  - kept adding tumours that were mismatched deficient and saw responses across tumours types

- The thinking started to change: maybe this genetic alteration is a more powerful indicator than were the tumour comes from
Enabling expedited development of transformative drugs - Keynote001

- Keynote trials are basket trials
- IND application submitted in Dec 2010
  - 8 protocol amendments
  - 1,235 patients recruited in 9 expansion cohorts
- 2 breakthrough therapy designations
- Pembrolizumab received accelerated approvals
  - In Melanoma in Sep-2014
  - In NSCLC in Oct-2015
Basis for FDA Accelerated Approval Pembrolizumab

149 patients with MSI-H/dMMR cancers enrolled across 5 uncontrolled, multi-cohort, multi-center, single-arm clinical trials

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>N</th>
<th>Objective response rate n (%)</th>
<th>95% CI</th>
<th>DOR range (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>90</td>
<td>32 (36%)</td>
<td>(26%, 46%)</td>
<td>(1.6+, 22.7+)</td>
</tr>
<tr>
<td>Non-CRC</td>
<td>59</td>
<td>27 (46%)</td>
<td>(33%, 59%)</td>
<td>(1.9+, 22.1+)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>14</td>
<td>5 (36%)</td>
<td>(13%, 65%)</td>
<td>(4.2+, 17.3+)</td>
</tr>
<tr>
<td>Biliary cancer</td>
<td>11</td>
<td>3 (27%)</td>
<td>(6%, 61%)</td>
<td>(11.6+, 19.6+)</td>
</tr>
<tr>
<td>Gastric or GE junction cancer</td>
<td>9</td>
<td>5 (56%)</td>
<td>(21%, 86%)</td>
<td>(5.8+, 22.1+)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>6</td>
<td>5 (83%)</td>
<td>(36%, 100%)</td>
<td>(2.6+, 9.2+)</td>
</tr>
<tr>
<td>Small intestinal cancer</td>
<td>8</td>
<td>3 (38%)</td>
<td>(9%, 76%)</td>
<td>(1.9+, 9.1+)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>PR, PR</td>
<td></td>
<td>(7.6, 15.9)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>PR, SD</td>
<td></td>
<td>9.8+</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>1</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>1</td>
<td>PR</td>
<td></td>
<td>18.2+</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>1</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal adenocarcinoma</td>
<td>1</td>
<td>PR</td>
<td></td>
<td>7.5+</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>1</td>
<td>CR</td>
<td></td>
<td>8.9+</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>1</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRC: Colorectal Cancer
Ref: FDA website
Larotrectinib FDA Approval

- Based on basket study results
- Treatment of TRK+ genetic mutation regardless of origin or site of cancer
- Impressive efficacy results with an 75-80% overall response rate (ORR)
- Data in first 55 patients with unresectable or metastatic solid tumors harboring an NTRK gene fusion enrolled across 3 multicenter, open-label, single-arm clinical trials
- A total of 12 cancer types were represented,
  - most common salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%) and thyroid cancer (9%)
Basis for FDA Accelerated Approval Larotrectinib

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Patients (N=55)</th>
<th>ORR</th>
<th>95% CI</th>
<th>DOR Range (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue sarcoma</td>
<td>11</td>
<td>91%</td>
<td>(59%, 100%)</td>
<td>3.6, 33.2+</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>12</td>
<td>83%</td>
<td>(52%, 98%)</td>
<td>7.7, 27.9+</td>
</tr>
<tr>
<td>Infantile fibrosarcoma</td>
<td>7</td>
<td>100%</td>
<td>(59%, 100%)</td>
<td>1.4+, 10.2+</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5</td>
<td>100%</td>
<td>(48%, 100%)</td>
<td>3.7, 27.0+</td>
</tr>
<tr>
<td>Lung</td>
<td>4</td>
<td>75%</td>
<td>(19%, 99%)</td>
<td>8.2, 20.3+</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4</td>
<td>50%</td>
<td>NA</td>
<td>1.9, 17.5+*</td>
</tr>
<tr>
<td>Colon</td>
<td>4</td>
<td>25%</td>
<td>NA</td>
<td>5.6*</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td>3</td>
<td>100%</td>
<td>(29%, 100%)</td>
<td>9.5, 17.3</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td>SD, NE</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Appendix</td>
<td>1</td>
<td>SD</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
<td>PD</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1</td>
<td>SD</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

- Safety was evaluated in 176 patients enrolled across the three clinical trials
- Identification of positive NTRK gene fusion status was prospectively determined
- Favorable risk/benefit profile
FDA Data Requirements Histology-Independent Indications

- Sufficient data to make a risk-benefit determination
- Sufficient data that the effect is “real”

Influenced by
- Scientific / biological rationale
- Magnitude of benefit
- Known toxicity profile
- Unmet need / lack of available therapies
- Risk to patient of no treatment
The European View: Possible in Theory, Challenging in Practice

- The concept of histology-independent indications
  - Requires in-depth knowledge about the mechanism and at least strong plausibility across subgroups
  - Need to explore heterogeneity of effects (interactions, resistance mechanisms)
  - Multiple therapeutic contexts, evidence of positive benefit-risk balance
  - Easier when high unmet need across subgroups
  - Challenging when competing against available options with established clinical utility (e.g. survival) in some subgroups; indirect comparisons (rare diseases, lack of historical data); extrapolation
How do complex data fit in regulatory decision making?

Adapted from Günter Heimann, Pharmacometrics Pediatrics
How can Modeling support paediatric drug development?

- With full or partial extrapolation, the objective is to transpose the adult label to children:
  - modeling can be used to demonstrate similarity between data from adult and pediatric patients
  - for example using the “predictive approach” (see next slide)
  - if similarity can be shown, this serves as additional evidence for extrapolation

- If extrapolation cannot be applied, use innovative statistical approaches:
  - e.g. statistical methods for rare diseases
  - e.g. statistical methods for sample size re-calculations
The predictive approach

1. Use adult data \((Y_A, E_A, C_A)\) to build a model \((P_A)\) which links exposure \((E_A)\) and baseline risk factors or other important covariates \((C_A)\) to the clinical outcome \((Y_A)\):
   \[
   Y_A = P_A(E_A, C_A) + \text{noise}
   \]

2. Use adult model and pediatric data \((Y_P, E_P, C_P)\) to predict outcome in children, conditional on observed exposure and covariates:
   \[
   Y^* = P_A(E_P, C_P) + \text{noise}
   \]

3. Compare predicted outcomes \((Y^*)\) with truly observed outcomes \((Y_P)\)
How to apply this approach in practice?

- For compound ABC where one wants to use **full extrapolation**, predictive approach can be applied to compound DEF external to ABC:
  - adult and children data are obtained from DEF
  - the predictive approach is applied to DEF
  - if the prediction approach works under DEF, it should work under ABC
  - no efficacy data in children will be collected for ABC
  - a small pediatric PK study is done for ABC to confirm dose selection (PK matching)

- For compound ABC where one wants to use **partial extrapolation**, predictive approach can be applied to ABC directly:
  - adult and children data are obtained for the compound ABC itself
  - the model is built based on adult data from compound ABC
  - a small pediatric study is conducted for ABC collecting PK & efficacy data, to confirm dose selection and to validate model by applying a predictive approach
Case study: Everolimus in Liver Transplantation

• **Background:**
  The PIP included single arm pediatric liver transplant trial:
  – 75 patients were to receive everolimus + reduced dose of tacrolimus;
  – same target exposure as adults;
  – somewhat different study design (everolimus added later in children)

• **Problem:** recruitment difficulties

• After 5 years, a request for modification of the PIP was filed

• **Proposal:**
  Apply “predictive approach” to support partial pediatric extrapolation, and submit interim results with at least 20 patients
Case study: Everolimus in Liver Transplantation

- Adult model had already been built for the adult submission
  - Primary endpoint: organ rejection
- At the time of the interim analysis, data from 22 pediatric patients were available
  - No organ rejections observed in these 22 children
- Use adult models to simulate outcome (= number of organ rejections) of 10000 pediatric studies with N=22 children
- Simulations used the observed covariates of the original N=22 children
- Model qualification: compare with observed outcome
Thank you
References


- FDA guidance

- EMA workshop

- CTFG guidance