Individual Drug Development (IDD)

From n=1 therapy to orphan drug-like development

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Disclaimer

- The views expressed here are those of the author.
  The proposals have not yet been formally discussed within the Medicines Regulatory Network.

The Challenge

- RNA technologies enable therapies starting in a single patient.
- Hyperindividual ASO therapies often begin as n=1 interventions
  but if successful may approach ‘orphan drug-like status’
- Current regulatory and research frameworks are not designed for this:
  - many stakeholders and responsibilities, different approaches and requirements
  - insufficient academic drug-development infrastructure
  - stepwise *ad hoc* development may lose essential regulatory information

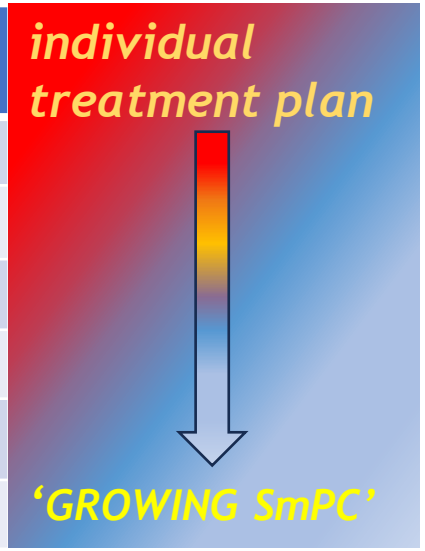
⟶ Lack of accepted development pathway and regulatory agreement

The Concept: ‘Individual Drug Development’

- Hyperindividual therapy as the first phase of drug development:

Parallels between Drug Development and Individual Treatment

Drug development phases	Drug development objectives	Individual treatment objectives
preclinical	drug target development	pathophysiological rationale
phase I	clinical pharmacology	dose selection / PK / route
phase II	biomarker improvement	biomarker / dosing optimization
phase III	clinical net benefit / risk	clinical benefit assessment
registration phase	market access	care / reimbursement decision
phase IV	post-marketing surveillance	registry follow-up



Key Features

- Individual Drug Development connects clinical care, research and regulation.
  - Enables systematic learning about RNA/DNA-Tx from individual *n=1* treatments
  - Creates a traceable evidence pathway
  - Facilitates transition from individual treatment to ‘orphan-like’ therapy
  - Supports collaboration across the medicines development and regulatory network
  - Prevents ‘indication creep’ and allows controlled clinical access/reimbursement

→ Structured academic innovation and early drug development
-with proportional ‘fit-for-purpose’ development/regulatory guidance
-aligned with accumulation of clinical experience from experimental use to therapy

Individual Drug Development Regulation Schema

• Development Steps	Governance	Guidance
n=1 treatment ↓ systematic learning ↓ *n-of-few* studies ↓ 'orphan drug-like' development ↓ clinical care	clinicians, translational scientists academic IDD-infrastructure consortia (RARE-NL, ATMP-NL, *etc*) 'Medicines Regulatory Network' ↕ CCMO/METC ↕ CBG-MEB, EMA ↕ health insurers, ZIN	*'IDD-Plan'* ↓ *templates, guidance docs, SOPs, platforms* ↓ *'Growing SmPC'* ↓ clinical practice guidelines, (biomarker/surrogate-based) reimbursement strategies

IDD Toolbox

- Accepted platform technologies:
  - Standardized production
  - Structured *in silico* analyses
  - Minimal fit-for-purpose preclinical safety package?
  - Class-based IB-template?
- Systematic IB-analysis of (failed/successful) RNA-Tx (CCMO/CBG/TNO)
- Individual Drug Development-templates:
  - Patient involvement ⟶ shared trajectory
  - Individual treatment plan:
    PK-PD (dose adaptation), follow-up (measurements), surrogates (clinical decisions), endpoints (care & costs)
  - Overall IDD-plan:
    phased protocols and amendments
- Databases
  - Scientific integration (‘model-informed drug development’)
  - Clinical registries
- Integrated governance structure (IDD-teams ↔ quality/GxP-infrastructure ↔ Medicines Regulatory Network)