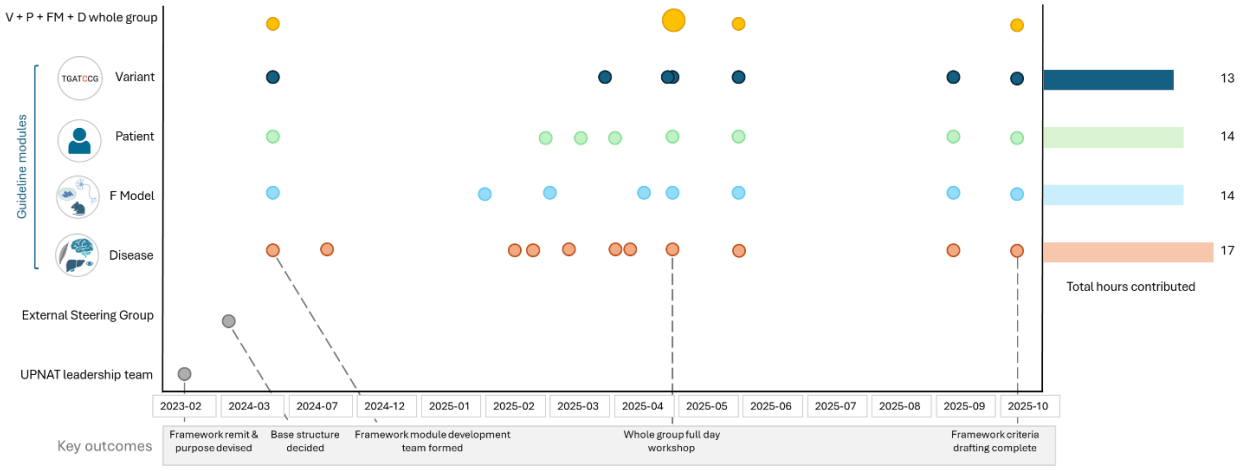
Supplementary Figures



Supplementary Figure 1: **Timeline of framework development.** Key dates in the framework development timeline, from initiation (2023-02) to a complete draft (2025-10). Dates and key outputs are described along the X axis, the contributing group is indicated on the Y axis and cumulative time spent on development for each module is shown to the right. The UPNAT leadership team consisted of six individuals, the external steering group was a multidisciplinary group of >30 expert scientists and clinicians with diverse NAT and rare disease expertise from across the UK, and the development leadership group consisted of nine multi-disciplinary colleagues split across four modules. This group was formed to achieve two pre-defined aims: 1) generating guidance for the selection of patients and targets for RNA therapies in the UK, and 2) facilitating implementation of this framework in select highly specialised services as exemplar.

Supplementary Tables

Supplementary Table 1: Expert group selected to develop the UPNAT target selection framework.

Individual	Designated section	Role	Institute/Company	Relevant expertise	Expert category
Dr Emma Clement	Disease	Leader	Great Ormond Street Hospital	Consultant in Clinical Genetics and Genomics Medicine specialising in paediatric rare disease with a focus on genetic deafness and deep knowledge of disease mechanisms and clinical presentations relevant to ASO therapy prioritisation.	Rare disease expert clinician, Clinical geneticist

Dr Hannah Titheradge	Disease	Leader	Birmingham Women's Hospital	Consultant clinical geneticist and Rare Disease lead for the Birmingham Women's Hospital with an in-depth clinical genetics background and experience in rare disease diagnoses, focusing on unmet medical need within NHS settings.	Rare disease expert clinician, Clinical geneticist
Prof Stephan Sanders	Functional model	Leader	Oxford University	Professor of Paediatric Neurogenetics and internationally recognised as an expert in human genetics, bioinformatics, and gene discovery, providing strong grounding in gene-level analysis.	Rare disease expert clinician, Academic molecular geneticist, Preclinical model development expert
Prof Jacqueline van der Spuy	Functional model	Leader	UCL	Professor of Molecular and Cellular Biology with specialist knowledge of inherited retinal dystrophies and experience in developing advanced functional models for fundamental science research and ASO preclinical development.	Academic molecular geneticist, Preclinical model development expert
Prof Carlo Rinaldi	Patient	Leader	Oxford University	Professor of molecular and translational neuroscience and Consultant Neurologist with extensive experience in translational research and clinical care of neurological diseases, providing expertise on patient-level feasibility and therapeutic applicability of ASOs.	Rare disease expert clinician, Academic molecular geneticist, Preclinical model development expert

Prof Manju Kurian	Patient	Leader	Great Ormond Street Hospital	Professor of Paediatric Neurogenetics and Consultant Paediatric Neurologist, internationally recognised for her work on childhood-onset neurogenetic disorders, bringing expertise in patient pathways, comorbidity assessment, and ethical considerations for early-phase ASO therapy.	Rare disease expert clinician, Academic molecular geneticist, Preclinical model development expert
Prof Jenny Taylor	Variant	Leader	Oxford University	Professor of Translational Genomics and Director the Oxford Biomedical Research Centre Genetics Theme, with expertise in variant interpretation, molecular diagnostics, and translational research, supporting rigorous variant-level assessment for ASO targeting.	Academic molecular geneticist, Preclinical model development expert
Dr Ana Lisa Tavares	Variant	Leader	Genomics England	Clinical Lead for Rare Disease research at Genomics England with specialist expertise in variant annotation and functional genomics, experienced in assessing variant pathogenicity and biological tractability in the context of precision therapeutic development.	Rare disease expert clinician, Clinical geneticist
Dr Nour Elkhateeb	Variant	Leader	Cambridge University Hospitals, Genomics England	Clinical Geneticist and Genomics England Research Fellow with expertise in genomics and transcriptomic, skilled in bioinformatic and laboratory-based evaluation of variant effects to inform their suitability for ASO intervention.	Rare disease expert clinician, Clinical geneticist

Dr Carme Camps	Variant	Developer	Oxford University	Molecular and computational biologist at Oxford University with expertise in genomic medicine and transcriptomics, combining bioinformatic and experimental approaches to interpret variant effects and assess their suitability for therapeutic intervention, including antisense oligonucleotide (ASO) strategies.	Academic molecular geneticist

Supplementary Table 2: Eleven market approved ASO therapies to calibrate and refine the UPNAT target selection framework.

Drug name	**Disease Target (MIM)**	**Gene Target**	**Assessor category**
Eteplirsen	Duchenne muscular dystrophy (310200)	*DMD*	Assessor 1: Academic molecular geneticist Assessor 2: Preclinical model development expert Assessor 3: Rare disease expert clinician
Nusinersen	Spinal muscular atrophy (clinical subtypes SMA 1-3) (253300, 253550, 253400)	*SMN2*	Assessor 1: Academic molecular geneticist Assessor 2: Preclinical model development expert Assessor 3: Rare disease expert clinician
Golodirsen	Duchenne muscular dystrophy (310200)	*DMD*	Assessor 1: Academic molecular geneticist Assessor 2: Preclinical model development expert Assessor 3: Rare disease expert clinician
Viltolarsen	Duchenne muscular dystrophy (310200)	*DMD*	Assessor 1: Academic molecular geneticist Assessor 2: Preclinical model development expert Assessor 3: Rare disease expert clinician
Casimersen	Duchenne muscular dystrophy (310200)	*DMD*	Assessor 1: Academic molecular geneticist Assessor 2: Preclinical model development expert Assessor 3: Rare disease expert clinician

Tofersen	Amyotrophic lateral sclerosis (SOD1 related) (105400)	*SOD1*	Assessor 1: Rare disease expert clinician, Academic molecular geneticist, preclinical model development expert Assessor 2: Academic molecular geneticist
Eplontersen	Hereditary transthyretin amyloidosis polyneuropathy (105210)	*TTR*	Assessor 1: Academic molecular geneticist Assessor 2: HCPC clinical scientist
Inotersen	Hereditary transthyretin amyloidosis polyneuropathy (105210)	*TTR*	Assessor 1: Academic molecular geneticist Assessor 2: HCPC clinical scientist
Olezarsen	Familial chylomicronemia syndrome	*APOC3*	Assessor 1: Academic molecular geneticist Assessor 2: HCPC clinical scientist
Volanesorsen	Familial chylomicronemia syndrome	*APOC3*	Assessor 1: Academic molecular geneticist Assessor 2: HCPC clinical scientist
Donidalorsen	Hereditary angioedema	*KLKB1*	Assessor 1: Academic molecular geneticist Assessor 2: HCPC clinical scientist

Supplementary Table 3: Application of the UPNAT framework across four illustrative patient case examples

Supplementary Tables 4: UPNAT disease assessment module.

Supplementary Tables 5: UPNAT functional model assessment module.

Supplementary Tables 6: UPNAT patient assessment module.

Supplementary Table 7: Variant module ASO amenability assessments for the patient cohort.