Nucleic Acid Therapeutics Initiative

RNA Drug Development –Hit2Lead

Information Deck

V0_17 Sep 2024

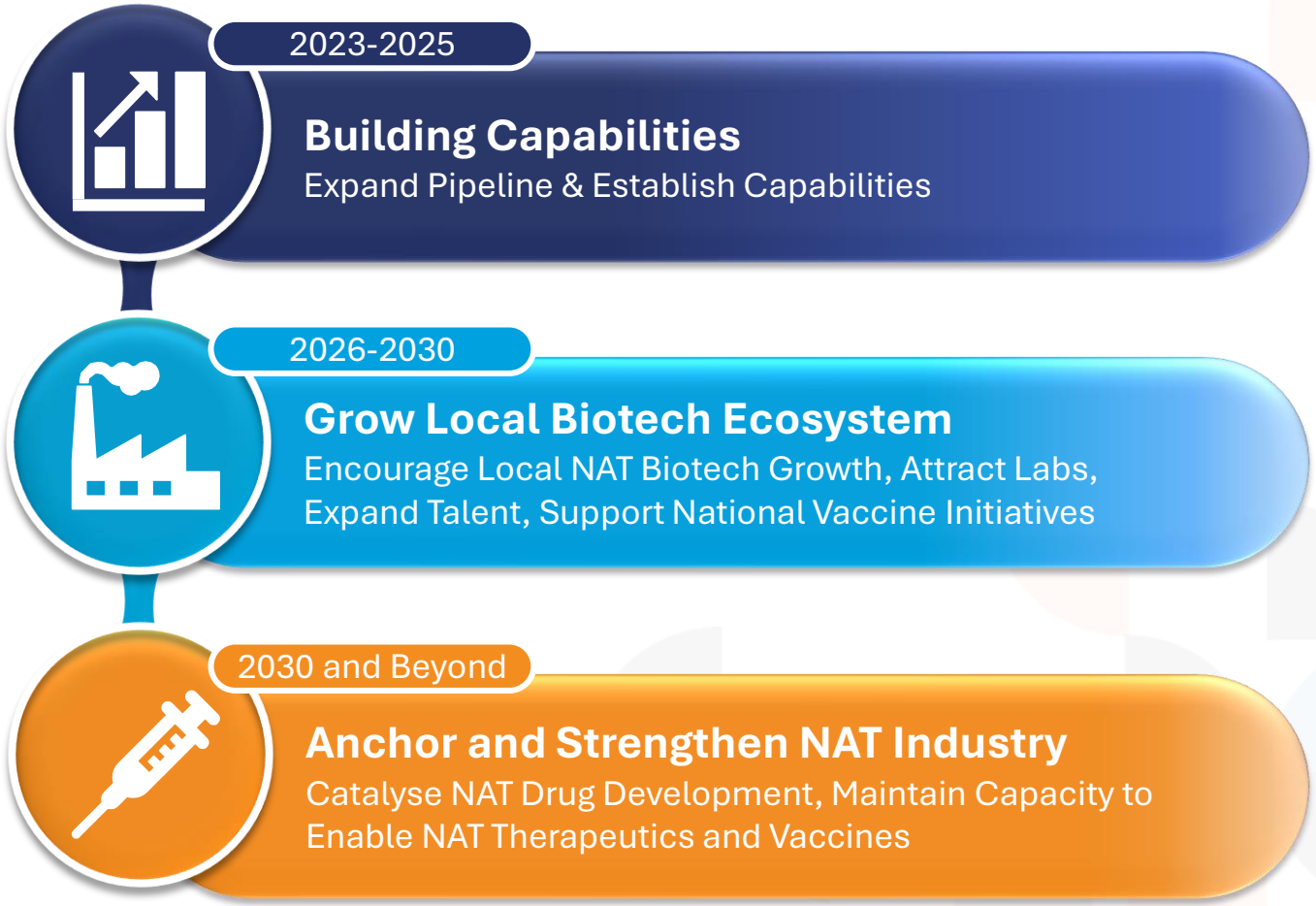
About NATi

(Pronounced "Net-eye")

To build Singapore into a regional hub for nucleic acid therapeutics research, clinical translation, and commercialisation.

NATi harnesses the potential of nucleic acids to **treat diseases using RNA molecules.** This initiative bolsters strategic partnerships and propels healthcare innovations, benefiting Singapore and Singaporeans.

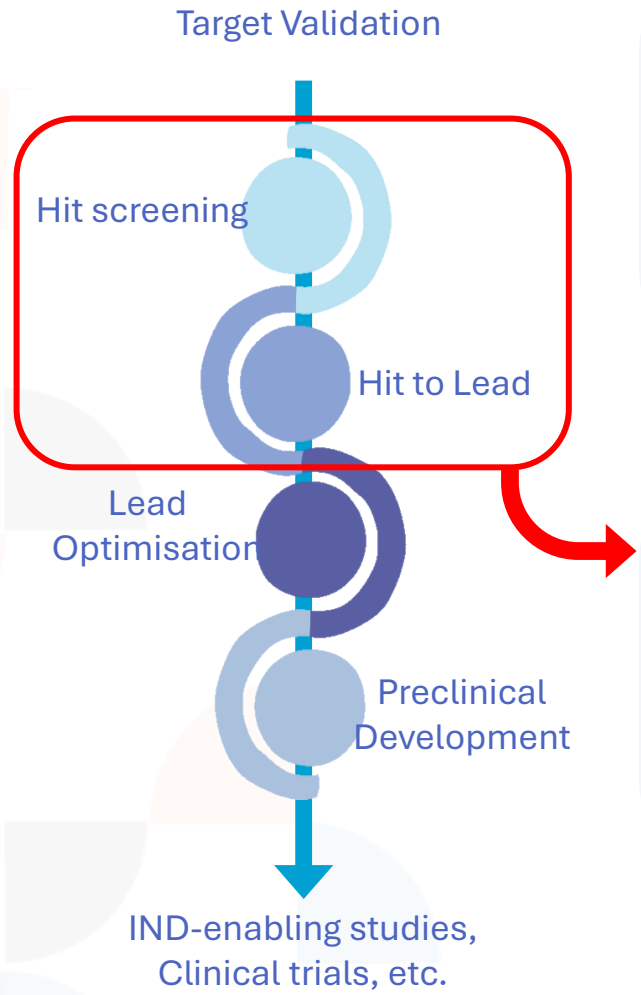
Outlook of SG NAT Activities



Legend: **RNA:** Ribonucleic Acid; **NAT:** Nucleic Acid Therapeutics

Objectives of NATi RNA Drug Development Hit2Lead

Drug Development Process

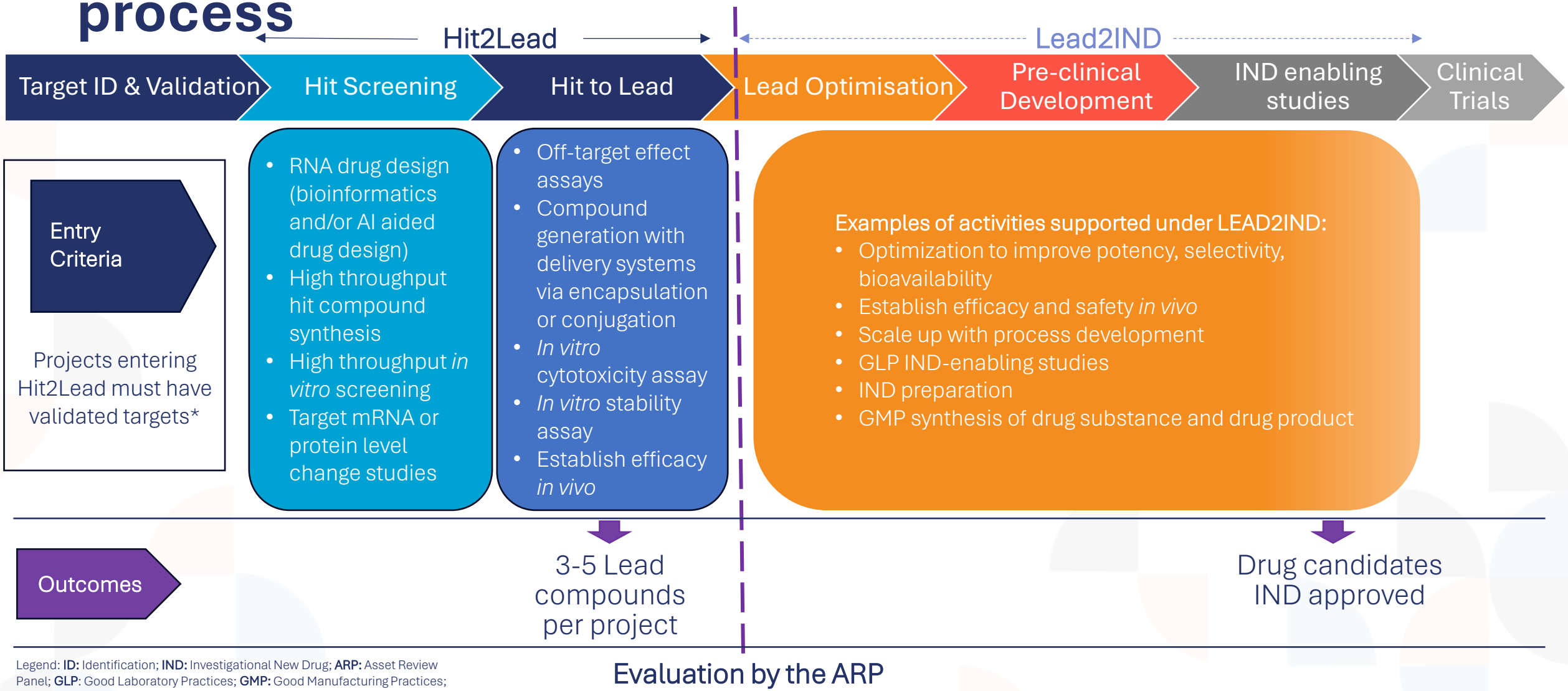


Legend: **IND:** Investigational New Drug

To accelerate the development of an RNA asset to Investigational New Drug (IND) filing and approval within a desired timeframe of ~3-4 years

Hit2Lead will support RNA drug development from hit generation to achieve lead compounds in 1 - 2 years.

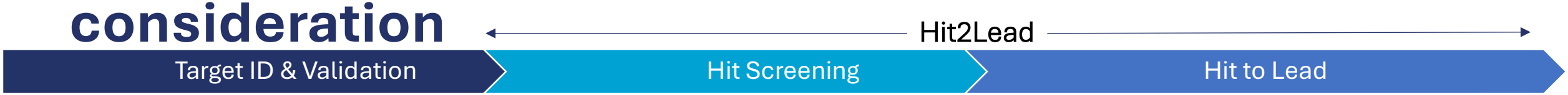
Overview of the drug discovery and development process



Legend: **ID:** Identification; **IND:** Investigational New Drug; **ARP:** Asset Review Panel; **GLP**: Good Laboratory Practices; **GMP:** Good Manufacturing Practices;
*refer to slide 6 for details on target validation

Follow on funding will be considered for promising Hit2Lead projects

Criteria for validated targets for Hit2Lead consideration



- *In vitro* expression and mechanistic studies
- Proof of pathway regulation in disease
- Assay development
- *In vivo* studies (e.g. target manipulation in disease models)
- Tool compound generation
- Target validation using patient-derived samples or consensus among *in vitro* models
- *In vivo* validation of efficacy with tool compound
- Interrogation of the selected target or pathway using tool compounds should be compared to publicly disclosed data in the same models to confirm the robustness of the *in vitro* and *in vivo* models proposed for the project

Criteria for validated targets:

1. Convincing evidence to show that the target is implicated in disease. It would be ideal if this is shown with patient-derived samples.
2. Quantitative demonstration (e.g. target knockdown efficiency) that the tool compound can modulate the target *in vitro*.
3. Quantitative and/or qualitative demonstration (e.g. improvements in surrogate markers) that the tool compound can modulate the target *in vivo*.

Legend: **ID:** Identification

Desired outcomes of Hit2Lead

Hit2Lead

Hit Screening → Hit to Lead

Hit Screening

- RNA drug design (bioinformatics and/or AI-aided drug design)
- High throughput hit compound synthesis
- High throughput *in vitro* screening
- Target mRNA or protein level change studies

Hit to Lead

- Off-target effect assay
- Compound generation with delivery systems via encapsulation or conjugation
- *In vitro* cytotoxicity assay
- *In vitro* stability assay
- Establish efficacy *in vivo*

1. When planning for Hit2Lead submission:
   - Articulate a target product profile (TPP) including a competitive landscape analysis needs to be presented
   - Design a series of robust *in vitro* assays
   - Select a feasible process to generate tool compounds
   - Articulate a path to IND approval in 3 – 4 years
2. Desired outcomes:
   - 3-5 Lead compounds that achieve all *in vitro* outcomes (efficacy, stability and toxicity) and *in vivo* efficacy outcomes that are listed in the target product profile
3. Follow on funding will be considered for promising Hit2Lead projects

Legend: **AI:** Artificial Intelligence; **IND:** Investigational New Drug

Application Requirements

Attributes of a Strong Application

Medical Need and Market Evaluation

- **Address an unmet need**
- **Differentiated** and significant benefit to current standard of care
- **A global market** and many opportunities

Research and Scientific Merit of Technology

- **Preliminary efficacy against a validated target** with strong hypothesis of MoA
- **Unique value proposition** with strong understanding of prior art
- **Acceptable safety profile** or plan for toxicity study

Clear Development Plan

- **Clarity** of a path towards first-in-human use
- Adequate knowledge of **regulatory path**

Commercialisation Plan

- Strong opportunities to create **intellectual property**
- Possibilities of **strategic partnerships**

Legend: **MoA:** Mechanism of Action

Target Product Profile (TPP) - “Start-with-the-end-in-mind”

Information typically contained in a TPP[1]

- **Indications**: Primary conditions, diseases, or states for which a drug can safely and effectively be used to address an unmet medical need
- **Population**: Which markets will the product be launched and which cohort of patients have the highest unmet need?
- **Clinical Efficacy**: Define objective efficacy endpoints with clear measures of success[2]. Define primary vs secondary endpoints. What would constitute a significant benefit over existing treatments?
- **Safety and tolerability**: Define the required safety profile as it compares to the standard of care. Define any specific adverse effects that need to be addressed.
- **Stability**: Any special storage requirements, and in use stability?
- **Route of Administration**: Benefit to the patient in terms of use, requirement for a delivery device, when will that be developed?
- **Dosing Frequency**: What is the current Standard of Care and the benefit of reduced frequency of dosing? Treatment duration (acute vs chronic)?
- **Cost**: Cost per dose target, commercial team modelling and timing for Health technology assessment (HTA)[3] engagement?
- **Competitive landscape:** Competitive analysis of the 1st therapeutic indication. Provide a clear description of the positioning of the proposed asset (i.e., First-in-Class vs Best-in-Class).

- The TPP outlines the desired ‘profile’ or characteristic of a target product that is aimed at a particular disease or diseases
- The TPP guides all of the disciplines involved in progressing a candidate from **discovery to First in Human, through pivotal trials to commercial.**
- The TPP is a living document: it should be reviewed at each stage of development to ensure the modality and indication remain viable against competitors on the market or in development
- Valuable tool, developed by FDA, to facilitate conversation between the regulatory organization and industry

1. Target Product Profiles in Pharmaceutical Development by KPMG
2. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics from FDA
3. Health technology assessment - Global (who.int)

Legend: **FDA:** Food and Drug Administration

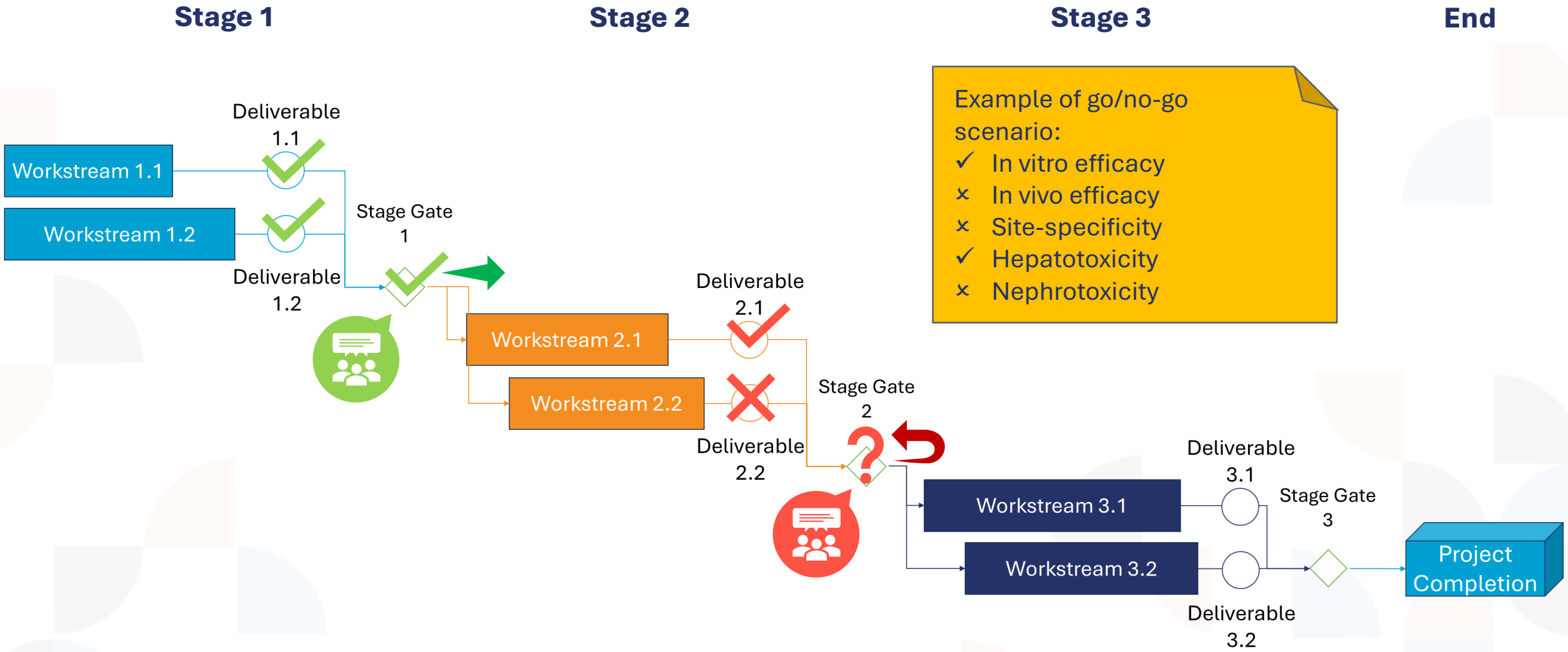
Evaluation Criteria

1. Medical Need and Market Evaluation
2. Research and Scientific Merit of Technology
3. Development Plans
4. Commercialisation and Intellectual Property
5. Experience and Expertise of the Team

Stage-gated project management is mandatory

Deliverables	Party responsible	Y1 Q1	Y1 Q2	Y1 Q3	Y1 Q4
Stage 1					
Workstream/Deliverable 1.1 e.g. Data driven RNA drug design					
Workstream/Deliverable 1.2 e.g. HT hit synthesis and screening					
Workstream/Deliverable 1.3					
Workstream/Deliverable 1.4					
Stage Gate 1					
Stage 2					
Workstream/Deliverable 2.1 e.g. in vitro toxicity screen					
Stage Gate 2					
Stage 3					
Workstream/Deliverable 3.1 e.g. Establish in vivo efficacy					
Final Report					

Stage-Gated Project Management – an Example



Eligibility

1. The Lead Investigator and Co-Investigators as defined in Grant Terms and Conditions should:
   a. Hold a primary appointment in a Singapore publicly funded research institution or an Institute of Higher Learning (IHL). The Lead Investigator must hold a primary appointment of at least 0.7 FTE in Singapore.
   b. Lead a laboratory or research programme which carries out research in Singapore
   c. Possess track record of leadership ability in coordinating research programmes and providing mentorship to research teams as well as having productive research outcomes. A track record in securing IRS will be advantageous.

2. Collaborators as defined in Grant Terms and Conditions are not eligible to receive NATi funding
   a. Companies can participate in NATi projects only as collaborators

3. Exceptions to the above eligibility criteria will be considered on a case-by-case basis. Please submit a request to the NATi Coordinating Office at least 7 calendar days before the submission deadline.

Legend:
FTE: Full-time equivalent; **IRS**: Industry R&D spending

Grant details

Funding Quantum

Up to S$2.5 Million (incl. 30% indirect costs)

Funding Duration

1 year

Eligibility

Singapore Public Sector Researchers (refer to slide 13 for full criteria)

Proposal submission deadline

29 Oct 2024, 12pm

Grant Scope

To support the development of RNA drug projects with validated targets to achieve lead compound optimisation in 1-2 years

How to apply

Email completed proposal, endorsement from Director of Research and budget sheet to enquiry@nati.sg

Application and Evaluation Process

Submission

- Lead Investigator submits proposal to enquiry@nati.sg by deadline
- Deadlines will be communicated in every thematic Call for Proposals

Review

- Lead Investigator may be invited to present
- Outcome of review will be communicated to the Lead Investigator within 5 – 6 months of proposal submission

Award

- After final budget review, successful applicants will be issued In-Principle Approval and subsequently a Letter of Award

Contact Us

For general enquiries, please contact:

enquiry@nati.sg