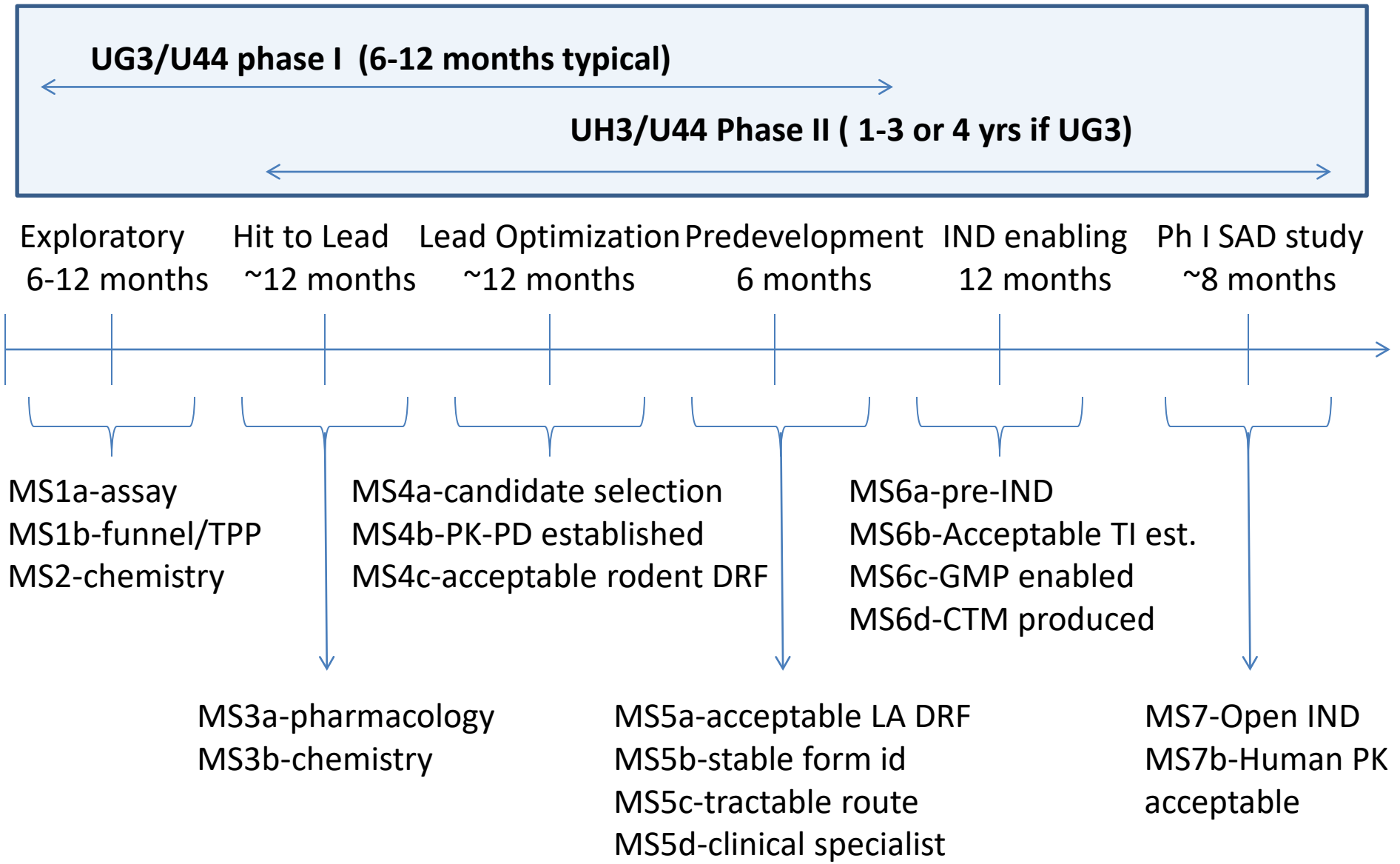
Disclaimer: For illustrative purposes ONLY. Milestones will be customized and project specific milestones added. It is strongly recommended you speak with Program Staff prior to application submission.

Note: The resources availability is not guaranteed and are customized to each project based on the resources being proposed within the grant budget.

National Institute of Neurological Disorders and Stroke

Milestone Progression by Stage



Grant duration maximum of 5 years for the combination of the both phases

Development Phase Projects

- Start of Compound Characterization Salt/Polymorph Screen and LA DRF
  - Required milestones MS1a/MS1b/MS2/MS3a/MS3b/MS4a/MS4b/MS4c
- Start of Non-GMP scale–up/GLP studies/GMP/CTM
  - Required milestones MS1a/MS1b/MS2/MS3a/MS3b/MS4a/MS4b/MS4c/MS5a-d
- Start of Ph I
  - Required milestones MS1a/MS1b/MS2/MS3a/MS3b/MS4a/MS4b/MS5a-d/MS6a-d

Milestones and BPN Resources Available by Stage from BPN

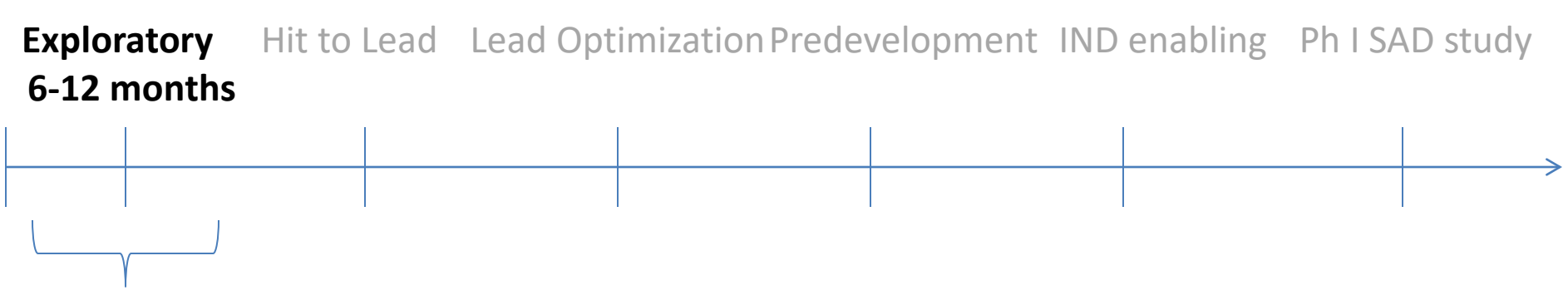
Exploratory Milestones (MS1a)

- Assay Milestone: Validate the primary assay for SAR.
  - Criteria for success:
    - Z' score of ≥0.5, based on values from at least half a plate of positive and negative controls
    - Concentration response testing over at least 8 concentrations generates reproducible EC_{50} values within a 3-fold range for at least 4 compounds
    - Blinded test-retest reliability with r^2 of at least 0.75 on at least 8 compounds exhibiting EC_{50} values across a 100-fold range of potencies.
    - Two independent, sequential runs achieve a throughput of at least 15 compounds per run with a maximum of two weeks between compound receipt and data entry into the CDD database. Data must include a full concentration response curve of at least 8 points for each compound tested.

BPN Resources Available

- **NIH Program and Science Officers**
- **BPN Assay Consultants**
- **Collaborative Drug Discovery (CDD) relational database access**

Exploratory Milestone (MS1b)

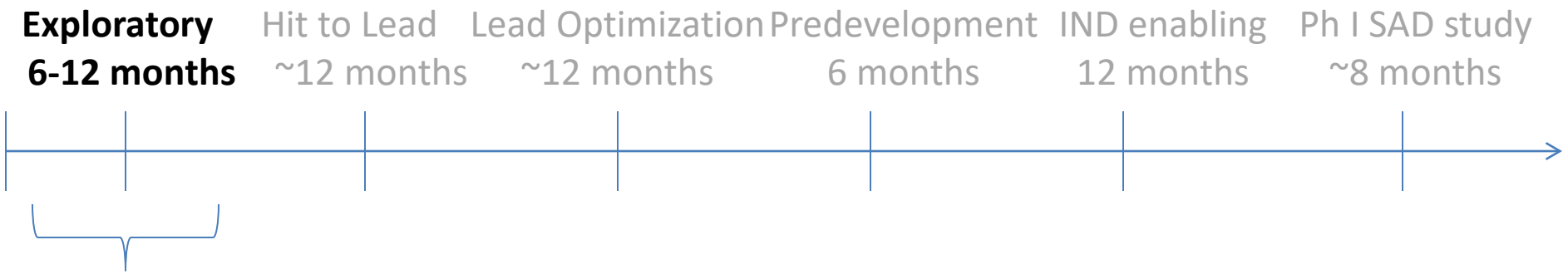


- Screening funnel finalized and all in vitro assays and in vivo assay plans in place to drive SAR program
  - Established Selectivity Assay and throughput
  - Established in vitro ADMET source and throughput
- Target Product Profile established and Steering Committee and NIH agreement established.

BPN Resources Available

- **NIH Program and Science Officers**
- **BPN Lead Consultants an addition to specialized assay Medchem and DMPK consultants**
- **Collaborative Drug Discovery (CDD) relational database access**
- **Limited access to PK/tox contract**

Exploratory Milestone (MS2)



Identify at least one lead series with demonstrated SAR.

- Criteria for Success:
  - Within the series, potencies of close compound analogs must be sub-micromolar and show values over at least a 50-fold range, with variations in potency over this range, including highly active, moderately active, and inactive compounds
  - Improvement in potency >10x over entry lead compounds
  - Improvements in physicochemical properties must be evident for some active compounds
  - Demonstrated SAR must be sufficient to formulate a data-driven strategy for multi-parameter optimization, improving physicochemical and ADMET properties in addition to potency
  - Demonstrate a clear path to develop IP around primary and demonstrate plans for a back-up series

BPN Resources Available

- **NIH Program and Science Officers**
- **BPN Medchem and DMPK consultants**
- **Relational database access (contract): Collaborative Drug Discovery (CDD)**
- **Medchem Contract: Curia resources. Level of efforts ~ 2.5 chemists for 6 months plus limited CADD and in vitro ADMET support***
- **Limited access to PK/tox contract**

* If all medchem funded via contract

Hit To Lead Milestones (MS3)

Exploratory | **Hit to Lead** | Lead Optimization | Predevelopment | IND enabling | Ph I SAD study

~12 months

Pharmacology

- Demonstrate in vivo activity of a representative compound from the lead series (any route of administration and does not require duration consistent with final compound)
  - Established In-vivo assay with sufficient capacity to drive program
  - Demonstrate activity at reasonable dose for translation
  - Assess improved therapeutic index or other benefit feasible

Chemistry

- SAR should meet perspective lead identification criteria.
  - Not necessarily all parameters in the same compound
  - Data should be compelling to formulate data-driven strategy to combine attributes into a single stereo- and enantiomerically-pure compound.
- Improve rodent oral bioavailability to >20% at ≤10mg/kg
  - Compound should not have confounding off-target pharmacology (at least 10x selectivity)
  - 100X selectivity over threatening off-target activities.

BPN Resources Available

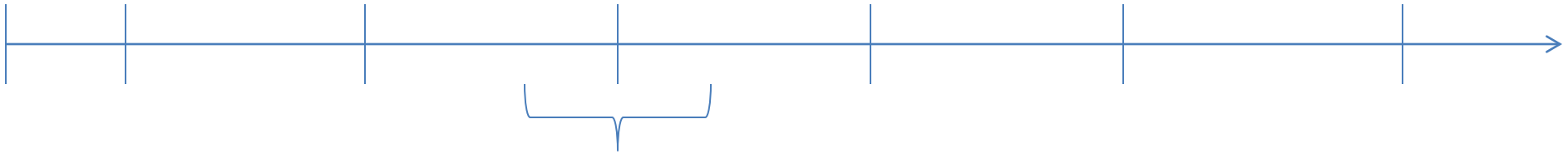
- **NIH Program and Science Officers**
- **BPN Medchem, Tox and DMPK consultants**
- **Collaborative Drug Discovery (CDD) relational database access**
- **Curia resources. Level of efforts ~ 4 chemists for ~12 months plus limited CADD and in vitro ADMET support***
- **Access to PK/tox contract**

* If all medchem funded via contract

Lead Optimization Milestones (MS4)

Exploratory | Hit to Lead | **Lead Optimization** | Predevelopment IND enabling | Ph I SAD study

~12 months



- **Candidate Selection**
  - Select a preclinical development candidate based on perspective criteria to advance into Dose Range Finding studies
    - Including multi-dose PK and large animal PK required to enable DRF's
    - evaluation of off-target activities, physical properties, scalability of synthetic routes.
  - Synthesize sufficient quantities to enable both rodent and large animal DRF's
  - Acceptable TI and predicted human dose:
    - Candidate selected based on comparison of the data from:
      - PK-PD experiments/*pharmacology* models (by intended route)
  - Patent position established (provide letter from attorney)
    - Verify patents filed and plan in place for national filings
    - Complete prior art search of available patent databases indicating the chemical structure searched to establish composition of matter and use
  - Rodent DRF is acceptable exposure and safety margin to support further non-clinical development

BPN Resources Available

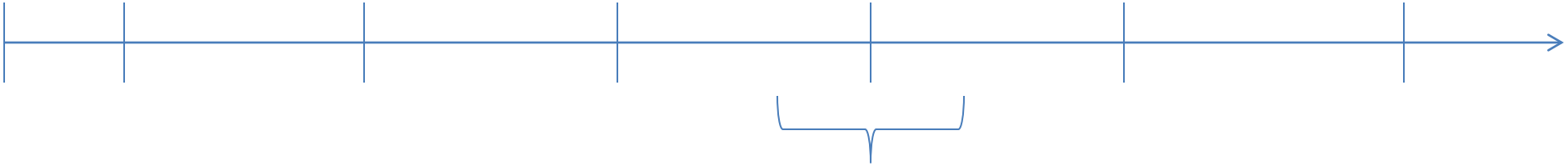
- **NIH Program and Science Officers**
- **BPN Medchem, Process Chemistry, CMC, Tox and DMPK consultants**
- **Collaborative Drug Discovery (CDD) relational database access**
- **Curia resources. Level of efforts ~ 4 chemists for ~12 months plus limited CADD and in vitro ADMET support***
- **Access to PK/tox contract**

* If all medchem funded via contract

Pre-development Milestones (MS5)

Exploratory Hit to Lead Lead Optimization **Predevelopment** IND enabling Ph I SAD study

6-12 months



- **Complete Candidate Characterization Completed**
  - Large Animal DRF results is acceptable exposure and safety margin to support further non-clinical development
  - DRF results provide adequate information for determination of doses for definitive IND-enabling toxicology.
  - Stable polymorph and salt selected
  - Suitable formulation established to enable IND work packages and Ph Ia
  - Provide a letter of support and engagement of a Clinical Specialist that will support early development activities of candidate and provide clinical subject matter expertise for completion of a Clinical Plan Outline through Phase 2.
  - Synthetic Route selection
  - Cost feasibility
  - Produce material for IND enabling studies (non-GMP)
- **Hold Pre-IND meeting as needed to assure proper GLP studies to enable Ph I trials**

BPN Resources Available

- **NIH Program and Science Officers**
- **BPN Process Chemistry, CMC, Tox and DMPK consultants**
- **Relational database access (Contract): Collaborative Drug Discovery (CDD)**
- **Drug Manufacture and Formulation Contract: MRI Global and Curia resources.**
- **Access to PK/tox contract**

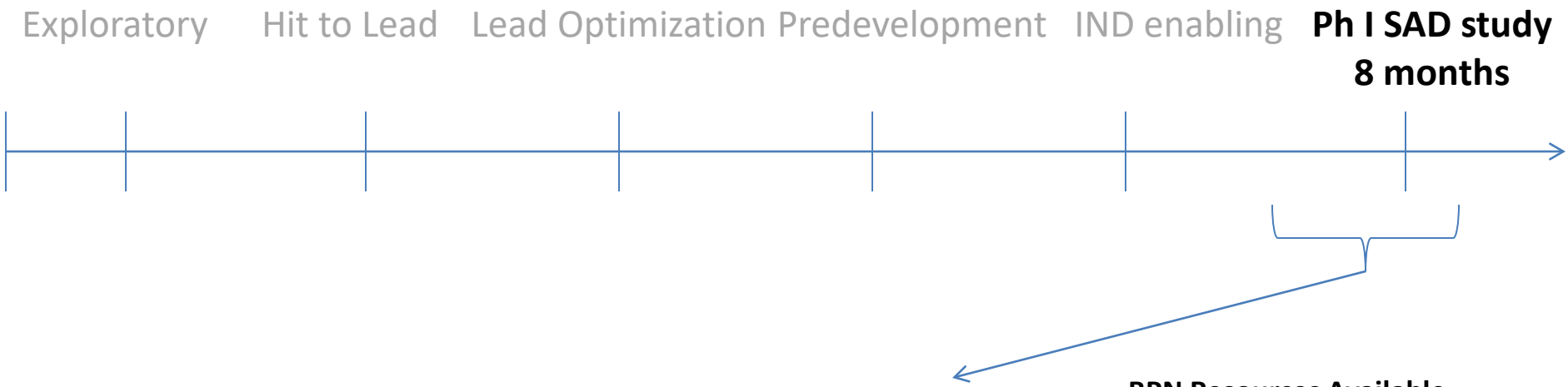
IND Enabling Milestones (MS6)

- **Development**
  - Complete activities necessary for IND filing.
- Criteria of success:
  - Complete GLP IND enabling studies:
    - Demonstrate sufficient safety margin to allow for progression to clinical trials
    - Based on preclinical evidence show that exposures achieved in the clinic should be sufficient to provide target modulation at the projected human dose
  - Overcome GMP scale up issues
  - Finalize and produce CTM
  - All reports finalized and IND compiled with exception of finalized protocol

BPN Resources Available

- **NIH Program and Science Officers**
- **BPN Process Chemistry, DMPK, CMC, Tox, Regulatory, clinical and consultants**
- **Drug Manufacture and Formulation Contract: MRI Global and Curia resources.**
- **GLP Toxicology through Contracts.**

Phase I Clinical Trial Milestones (MS7)



- Pre-IND meeting Complete
- Conduct Phase I single ascending dose trial
  - Obtain IND for trial
    - Work with CRO to Finalize protocol and assemble necessary documents for IND e.g. 1571, 1572, 3674 etc.
    - Obtain IRB approval for protocol
    - IND Filing and approved
  - Commence trial

BPN Resources Available

- **NIH Program and Science Officers**
- **BPN Process Chemistry, DMPK, CMC, Tox, Regulatory, clinical and consultants**
- **Clinical Trial contract for Phase I activities (PPD/DCRI)**