Topic: Improving the preclinical prediction of adverse effects of pharmaceuticals on the nervous system

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Neurotoxicity (used in the context of this document as “any adverse effect on the Central Nervous System (CNS) or Peripheral Nervous System (PNS)”) is poorly predicted by preclinical studies performed on pharmaceuticals during Research and Development (R&D) process. As a consequence, adverse effects on nervous system are not uncommon during clinical development and post-marketing. This lack of predictability might have two types of consequences:

- For human volunteers/patients, this can lead to a risk of adverse effects during clinical trials or even after marketing;
- For the Pharmaceutical Industry, this can lead to substantial neurotoxicity-related attrition rates, generally at late stages (clinical phase 2 or 3); the figures for this type of attrition are variable according to sources, but are typically in the range of 5-25%.

Therefore, a better preclinical prediction of adverse effects on nervous system would benefit to human volunteers/patients (safer drugs) and Pharmaceutical Industry (increased productivity).

There are various reasons for poor prediction/detection of adverse effects on the nervous system at preclinical stages. The challenges relate to the following considerations:

- The brain is the most complex organ in the body, comprising numerous cell types and functions;
- Full knowledge is lacking about the chain of events (molecular, subcellular, cellular, tissue, organ-level) and their timing leading to neurotoxicity;
- No robust *in silico* tool is available to establish (quantitative) structure-toxicity relationship;

- No *in vitro* cellular/tissue system is widely accepted/validated for screening;
- There is a lack of predictive *in silico* simulation or *in vitro* test system to predict blood-brain-barrier penetration or exposure of target tissues;
- Traditional neurotoxicity testing in animal models is generally limited to symptoms (with lack of specificity), EEG (with inconsistent interpretation) and histopathological investigations (with lack of sensitivity) that are late endpoints, detecting rather severe effects;
- Sensitivity and translatability to the human condition of each animal species is not clearly established;
- No soluble biomarkers of neurotoxicity are formally validated or even identified yet.

Under the wide umbrella of "neurotoxicity", at least three types of effects are even more challenging in terms of preclinical prediction and translation to human situation:

- Seizures/convulsions, thus further epileptogenic events/epilepsy;
- Psychological/psychiatric changes: memory impairment, mood disorders, suicidality;
- Peripheral sensory neuropathies (this may include optic/auditory nerve).

Recent scientific and technical developments in neurosciences have been made that raise hope for the future, especially in the field of *in vitro* [1] and *in vivo* [2] models, translational biomarkers [3] or risk assessment [4] eg: *in silico* modelling of the blood-brain-barrier, use of (embryonic or human induced pluripotent) stem cells, single-cell analysis, organs-on-chips, measurement of micro RNAs or post-transcriptional (eg RNA editing) biomarkers.

Consequently, there is a clear need for a project to deliver on: (i) increased knowledge on mechanisms of neurotoxicity (eg establish Adverse Outcome Pathway for each type of neurotoxicity); (ii) better understanding of factors that favour neurotoxicity (pharmacological targets and pathways, physico-chemical properties, pharmacokinetics); (iii) implementing new-found knowledge to improve the current preclinical toolbox, through a combination of high throughput, predictive *in silico*, *in vitro* and *in vivo* models, including safety biomarkers where appropriate (iiii) combine these tools in an integrated risk assessment approach for better decision-points throughout R&D process, and better protection of human volunteers and patients.

Need and opportunity for public-private collaborative research

Research for improved predictive preclinical tools necessitates (i) expansion of knowledge regarding physiopathology of neurotoxicity: individual genetic/epigenetic susceptibility, role of blood-brain-barrier (under normal and pathological situations), non-neuronal and neuronal interplay, protection factors, receptors and neurotransmitters involved, novel safety biomarkers, functional changes as precursor of lesions, thresholds for effects (ii) establishing, testing and validating new/improved *in silico*, *in vitro* and *in vivo* models.

It is clear that such a wide range of complex questions can only be addressed via a public-private multi-stakeholder consortium, bringing their diverse expertise in the following fields:

- *in silico* modelling;
- cellular culture (especially stem cells and organs-on-chips);
- 'omics, systems biology/toxicology;
- imaging;
- single-cell analysis;
- electrophysiology;
- animal models (especially behavioural investigations);
- predictive biomarkers.

These expertise could be addressed by the following type of public-private stakeholders:

- Research Organizations and Universities would better contribute in the field of fundamental research, biomarkers identification, data management (especially when data in the precompetitive field will be shared) and project management/logistical/administrative support;
- Small- and Medium-sized Enterprises (SMEs) would better contribute in the field of *in silico* and *in vitro* tools;
- Pharmaceutical industry would better contribute in the field of *in vivo* studies, drug testing, historical data, reference and test compound supply;
- Patient Associations could join as partners, especially in the field of therapeutics indications where adverse effects on nervous system could be viewed as more frequent (psychiatry, oncology, neurology, immunology) as well as providing access to disease-specific donor material for in-vitro (primarily iPSC-related) work.

Lastly, a joint public-private project engaging key stakeholders' expertise could provide Clinicians and Regulatory Bodies with robust data for possible evolutions in the regulatory field. As appropriate, these potential partners will be asked to contribute, e.g. through participation to the Advisory Board.

Scope

The objective of the project is to improve the preclinical predictivity of adverse effects of pharmaceuticals on the central and peripheral nervous systems through increasing our knowledge on mechanisms of neurotoxicity and improvement of the experimental toolbox. The results would be an integrated prediction/evaluation approach that would include a combination of *in silico*, *in vitro* and *in vivo* models, including safety biomarkers (for peripheral neuropathies). This toolbox would increase the preclinical prediction of adverse effects of drugs throughout all aspects: identification of hazards, characterization of mechanisms of toxicity, prediction of clinical consequences and possible follow-up in trials with safety biomarkers, and integrated risk-assessment approach for proper decision-making process.

The adverse effects in the following areas of test articles should be considered by the applicants:

- Any pharmaceuticals under research and development stages. Not only small molecules are in the scope of the present topic, since biotherapeutics can lead to adverse effects on nervous system, directly or indirectly:
    - in a recent search performed by Abbvie on FDA/EMA labels in 2015, about 40% of biological products (vaccines, recombinant proteins, monoclonal antibodies) had mention of two or more neuropsychiatric adverse events in approval documentation/label. In the field of oncology, antibody drug conjugates can also lead to similar safety risks than small molecules.
- Drugs that pass blood-brain-barrier (BBB) but also drugs that do not overtly pass the BBB, since (i) passage can be very low but still have consequences, especially if accumulation or microglia-based responses occurs in the brain (ii) passage can be increased under various pathological conditions (infection, inflammation, neurodegenerative diseases).
- Whether the indication is CNS or PNS or not: off-target pharmacology can often be responsible for adverse effects on nervous effect independently of the desired on-target action, as shown in a recent publication : out of 70 targets that have established linked with adverse effects, 50 (71%) relate to nervous system [5]. As an example, modulation of inflammation can lead to mood disorders, as illustrated by interferon effects.
- Biomarkers of peripheral neuropathies

Should not be considered by the applicants:

- Vaccines, because of specific development plans and regulatory requirements.
- Recreational drugs.
- Drug Abuse Liability Assessment (DALA) since it is already addressed by international guidelines.

- Biomarkers of central neurotoxicity which might be covered in another IMI2 project and in an ILSI-HESI initiative on translational biomarkers of neurotoxicity (NeuTox).

Expected key deliverables

With the aim of improving the predictivity of the preclinical toolbox for assessment of neurotoxicity, the following deliverables are expected:

- **Deliverable 1:** new/improved *in silico* tools that allow establishing (quantitative) structure-activity relationship ((Q)SAR), "activity" meaning here neurotoxic effects.

  These tools would permit identifying "neurotoxicophores" and thus help companies to build chemical structures devoid of neurotoxic liabilities, as early stages of research (selection of best (pre-)candidates or chemical series)
- **Deliverable 2:** better understanding, modelling and simulation of the blood-brain barrier passage or exposure of target organs (brain, nerves), including for biologics and novel drugs used for focal disease interception.
- **Deliverable 3:** at least one new/improved *in vitro* tool for screening (pre-)candidate drugs for each type of toxicity tackled in this topic, especially using stem cell systems and organs-on-chips.
- **Deliverable 4:** at least one tool for elucidating mechanism of toxicity (target, pathway), especially using stem cell systems and organs-on-chips.
- **Deliverable 5:** new improved *in vivo* animal models, with more specific investigational endpoints, allowing focused, non-invasive detection and longitudinal follow-up of the central and peripheral nervous toxicities during drug development.

  Ultimately, this might help change regulatory requirement for entry into phase 1 (safety pharmacology assessment of central nervous system, as described in ICH-Safety guideline)
- **Deliverable 6:** better characterization of the most relevant animal species for each type of toxicity.
- **Deliverable 7:** identify and validate safety biomarkers predictive of peripheral nervous system toxicity, translatable from pre-clinical testing (*in vitro* and animal) to humans, and that do not necessitate cerebrospinal fluid sampling.
- **Deliverable 8:** integration of the deliverables in a Pharmacokinetic/Pharmacodynamic/Toxicodynamic (PK/PD/TD) platform with appropriate quantitative and qualitative decision points for risk assessment.
- **Deliverable 9:** Improved toolbox, especially for early, non-animal testing which would fulfil the 3Rs objective (Reduction/Refinement/Replacement).

Expected impact

At the level of R&D, regulatory, clinical and healthcare practice the impact would be (i) safer drugs for human volunteers/patients (ii) shortened development timelines through reduced attrition, reduced testing, and shortened development plans:

- Improved subjects/patients safety during clinical trials and after marketing authorization;
- Reduced attrition, especially at late stages of R&D (during clinical trials), for safety reasons related to neurotoxic effects;
- Reduced post-marketing events necessitating labelling changes;
- Reduced post-marketing events resulting in drug withdrawal;
- Greater R&D productivity/shorter timelines;
- Lower development costs.

In terms of ethics/animal welfare/3Rs, innovation and integration of new knowledge the impact would be:

- Replacement: whenever possible animal models would be replaced by *in silico/in vitro* models, provided they have at least the same level of prediction;
- Refinement and Reduction: relevant biomarkers or any other appropriate endpoints would enrich current *in vivo* animal experiment and help (i) earlier detection and longitudinal follow-up of toxicities before inappropriate animal suffering (ii) decision-making process;

In terms of improving European citizens' health and wellbeing (volunteers and patients), the impact would be:

- Lower risk of neurotoxic events during clinical trials, whatever the clinical indication (relating to nervous system or not);
- Improved monitoring and risk minimization procedures during clinical trials;
- Drugs with a better risk/benefit ratio.

In terms of industrial competitiveness the applicants should indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

The following completed, ongoing or forthcoming initiatives (the list is not exhaustive) have been identified and could be considered by the applicants:

- **FP7-HEALTH project PREDICT-IV** (http://cordis.europa.eu/result/rcn/148238_en.html)

  The objective was profiling the toxicity of new drugs: a non animal-based approach integrating toxicodynamics and biokinetics. Two neuronal primary models were analysed → the workpackage on convulsions/seizures could be relevant.

- **FP7-HEALTH project NEUROBID** (Neuroscience on barrier in development) (http://cordis.europa.eu/result/rcn/57029_en.html)

  One axis of research is to understand the involvement of normal and disturbed BBB function in normal and abnormal brain development → the entire project could be relevant

- **HESI Committee on Translational Biomarkers of Neurotoxicity** (NeuTox) http://hesiglobal.org/committee-on-translational-biomarkers-of-neurotoxicity/

  The objective is to identify biomarkers for improving the prediction of neurotoxicity → the workpackages 1 (*in vitro* prediction of electrical abnormalities) and 2 (peripheral neuropathies) could be relevant.

- **NC3Rs CrackIt challenge 17 Neuratect** (https://www.crackit.org.uk/challenge-17-neuratect)

  The objective is to generate physiologically-relevant human stem cell-based model(s) to identify neurotoxicity and seizure liability (neuronal viability/functional impairment) *in vitro* → the workpackage on convulsions/seizures could be relevant.

- **IQ Consortium on Preclinical Suicidality** (https://iqconsortium.org/initiatives/working-groups/preclinical-suicidality/):

  The goal is to provide an expert assessment of the science of preclinical evaluation of treatment-emergent suicidality → the workpackage on psychological changes could be relevant.

- **IQ consortium on MicroPhysiological Systems** (co-initiative with NIH) https://iqconsortium.org/initiatives/working-groups/microphysiological-systems-iq-nih-collaboration/

  The workpackages on convulsions/seizures and peripheral neuropathies could be relevant.

Please note that during the project implementation phase the applicants should also consider other potential knowledge generated by the forthcoming projects under IMI2 in the area of blood brain barrier, biomarkers of central nervous system toxicology, integrative knowledge management approaches, as well as the ongoing IMI initiatives:

- **TransQST** – for the use of quantitative systems toxicology (http://www.imi.europa.eu/content/trans-qst)
- **EBiSC** (European Bank for induced pluripotent Stem Cells) (http://www.imi.europa.eu/content/ebisc)

Industry consortium

The industrial participants will contribute through their expertise, data and resources, and materials especially (i) direct Full-Time Employees, (ii) data valorisation (iii) cash contribution (iv) material/reagent/consumable contribution.

Expected contribution from Industry consortium:

- Perform retrospective search into preclinical and pharmacovigilance databases to assess the incidence and nature of effects, and evaluate the predictability of current preclinical toolbox;
- Provide necessary number and diversity of drugs for validation of models;
- Provide retrospective data on reference or proprietary drugs that have showed neurotoxicity issues, preclinically or clinically;
- Run prospective assays/studies with drugs under development;
- Data and samples management:
    - expertise in samples and data management (including eg automated analysis of EEG);
    - database information and assessment;
    - biostatistics/programming;
    - provide data and samples from pre-clinical and clinical fields;
    - it is worth noting that competitive data would be shared to processes that will ensure protection of confidentiality/anonymity.
- Coordination and communication:
    - project management support with project design and day-to-day operation;
    - legal expertise scientific background to support regular review of deliverables regarding quality and operational ability.

Applicants should also note the detailed description of the industry contribution under “Suggested architecture of the Full Proposal”.

Indicative duration of the action

The indicative duration of the action is 36 months.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium

in preparation of the full proposal for stage 2. This may require mobilising, as appropriate, the following expertise:

- Systems toxicology/biology for the identification of mechanism of peripheral and central neurotoxicities;
- Conception of *in silico* tools for the identification of neurotoxicophores and (Quantitative) Structure-Toxicity Relationship;
- Building of dedicated modelling and simulation models of blood-brain-barrier passage supported by appropriate tools and databases;
- *In vitro* screening of neurotoxicity using human stem cell-derived systems;
- Organ-on-chip: brain, nerve;
- Animal neurotoxicity and neurobehavioral testing (including EEG, connection between cardiovascular function and convulsions…);
- Safety biomarkers identification and bioanalysis;
- Data management, data mining, biostatistics;
- Project management.

Expected contribution from applicant consortium

The academic partners, Research organisations and Universities could potentially bring:

- Scientific input to better understand parameters that lower the seizure threshold, and the transformation of seizure into convulsions;
- Identify pharmacological targets and biological pathways involved in the neurotoxic effects (on-target and off-target);
- Identify physicochemical parameters that correlate (and allow prediction) of blood-brain-barrier passage;
- Propose biomarkers of peripheral neuropathies.

The contribution from SMEs can be of great benefit to IMI2 JU projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal, if relevant. Under this topic, the contribution of SMEs could be beneficial for the following activities:

- Propose innovative assays/techniques for detection of neurotoxic effects: stem cells, organs-on-chip, subcellular systems (synaptosomes, mitochondria…), micro-electrode array technology, continuous video monitoring in rodents and non-rodents, live-brain imaging of neuronal activity;
- Run prospective assays/studies with reference drugs;
- Data and samples management:
  - data management: data access and data cleaning expertise;
  - biostatistics/programming: data analysis and programming expertise.
- Coordination and communication:
  - ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, budget management, etc;
  - ensuring the communication and dissemination with and/or media expertise and in developing tools.

The patient organisations, clinicians could potentially:

- Identify indications, pathologies, treatments for which neurotoxicity is a more critical issue.

The Regulatory Bodies could:

- Give feedback on tools, strategies, biomarkers that are proposed and their possible implementation in official guidelines.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating full proposal architecture, taking into consideration the industry contributions and expertise provided below.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

Work package 1 – Convulsions and Seizures

The goal of the work package "Novel methods and assays to predict seizures, convulsions and epileptogenesis" is to better detect pro-convulsant and convulsant compounds, using a combination of in silico (modelling, QSAR), *in vitro* and *in vivo* methods, including:

- ***In silico* models**

To develop and evaluate suitable *in silico* models to detect the potential for convulsions/seizures in drug development candidates. Such models may include systems biology/toxicology tools based on analysis of targets and pathways involved in such changes, as well as (Q)SAR systems that could help identifying toxicophores, based on physicochemical properties or peculiar exposure patterns in brain structures.

- ***In vitro* / *ex vivo* models**

To build on existing models and define their context of use for early *in vitro* / *ex vivo* detection of pro-convulsant / convulsant compounds. The aims of this work package are to (1) improve the performance of *in vitro* models while moving away from and minimizing the use of animal models with alternatives such as human iPSC-based neuronal tissue cells, and (2) define the context of use for various models; 3D models employing multiple cell types may be more physiological relevant, but this comes at a cost with material, time, resources, etc. Models will be specifically challenged to define their relative utility over each other and to provide guidance on when they should be employed. Effort will be directed toward creating robust, reproducible, and translatable models with clear benefits in these areas over existing current, commonplace models. Efforts can include 2D and 3D models using multiple relevant cell types, i.e. GABAergic and glutamatergic neurons, astrocytes, microglia, etc.

  - Applicant Consortium: will contribute expertise in *in vitro* neuronal network (2D and 3D), electrophysiology, and systems analytical skills and expertise which may contribute to the development of seizurogenic and pro-convulsant assays for detecting CNS-based electrical perturbations. Collaborators will develop appropriate assays and then evaluate their performance

using a variety of drugs with known pre-clinical and clinical effects to assess sensitivity, specificity, and utility of the *in vitro* assay(s).

- Industry Consortium: will contribute expertise in *in vitro* assay development, cellular material, and retrospective data on reference or proprietary drugs that have shown convulsant / electrical neurotoxicities in preclinical and clinical settings.

- ***In vivo* models**

The aims of this work package are to improve the performance and the specificity of *in vivo* models, especially through the refinement of endpoints in safety pharmacology and toxicology studies.

- Applicant Consortium: will contribute expertise in animal models of seizure and/or EEG signal processing which may contribute to the development of relevant tools for detecting convulsions/seizures (eg automated home cage detection of convulsive behaviours in rodents using continuous video monitoring, EEG signal processing, live-brain imaging of neuronal activity, etc.). This could be extended to non-rodents. Collaborators will develop appropriate tools/assays/endpoints and then evaluate their fit-for-purpose performance using a variety of drugs to assess sensitivity and specificity. "Non-classical" animal species could be considered (eg zebrafish).

- Industry Consortium: will contribute expertise in the conduct and analyses of *in vivo* animal studies, and retrospective data on reference or proprietary drugs that have shown seizurogenic/convulsant issues, both preclinically and clinically. Classical animal species for toxicology (rodent/non-rodent) will be considered as part of safety pharmacology/toxicology study packages as well as biological samples and/or raw data to partners for analysis.

Work package 2 – Psychological/psychiatric changes

The goal of this workpackage is to establish *in silico* (modelling, QSAR) and *in vitro* techniques and animal *in vivo* models for a better detection/prediction of psychological/psychiatric changes that may occur in clinical trials, including: memory and cognition disorders, mood disorders (including suicide ideation and behaviour).

- *In silico* and *in vitro* models

To develop and evaluate suitable *in silico* models and *in vitro* assays to detect the potential for psychological/psychiatric changes in drug development candidates. In silico approaches may include systems biology/toxicology tools to identify targets and pathways that are involved in psychiatric/psychological changes. In vitro assays may include iPSC-derived neurons to identify early molecular signals that may predict development of such adverse effects.

- Applicant consortium: will contribute expertise in *in silico* neurotoxicity expertise or *in vitro* neuronal cell assay development expertise which may contribute to the development of relevant tools for detecting psychological/psychiatric disorders. Collaborators will develop appropriate tools/assays and then evaluate their performance using a variety of drug to assess sensitivity and specificity.

- Industry consortium: will contribute expertise in *in vitro* assay development, and retrospective data on reference or proprietary drugs that have shown psychological/psychiatric issues, both preclinically and clinically.

- ***In vivo* models**

To develop and evaluate preclinical models that model features and traits of memory, cognition or mood disorders (including suicidal ideation and behaviour). Perform proof of concept in nonclinical models with known drugs. Evaluate their ability to translate across nonclinical species with potential to predict psychological/psychiatric changes in humans.

- Applicant consortium: will contribute expertise in animal models of memory, cognition and mood which may contribute (rat, dog, and non-human primates). Studies or endpoints will need to be established if not commercially available, and have some level of fit-for-purpose validation conducted.

- Industry consortium: will contribute expertise in animal studies, especially neurobehavioral endpoints, in rats, dogs and non-human primates.

Work package 3 – Peripheral Neuropathies

The goal of this work package is establish *in vitro* methods to detect peripheral neuropathy risk in drug development candidates, and to identify and evaluate safety biomarkers to monitor peripheral neuropathy in vivo for nonclinical use and translation to the clinical.

- ***In Vitro* models**

To develop and evaluate suitable *in vitro* assays to detect the potential for peripheral neuropathy in drug development candidates. Such models may include iPSC-derived sensory neurons with peripheral neuron character that can be used to screen drugs and detect toxicity or identify early molecular signals that may predict development of peripheral neuropathy.

- Applicant consortium: will contribute expertise in *in vitro* neuronal cell assay development expertise which may contribute to the development of relevant assays for detecting peripheral neuropathies. Collaborators will develop appropriate assays and then evaluate their performance using a variety of drug to assess sensitivity and specificity of the *in vitro* assay.

- Industry consortium: will contribute expertise in *in vitro* assay development, and retrospective data on reference or proprietary drugs that have shown peripheral neurotoxicity issues, both preclinically or clinically.

- ***In Vivo* models and safety biomarkers**

Candidate biomarkers should have some level of evaluation in preclinical models that demonstrates their association with peripheral neuronal cell degeneration/necrosis. Depending on the nature of that evaluation, promising biomarkers may need additional proof of concept in nonclinical models with known induced peripheral neuronal injury. In addition, candidate biomarkers should be selected for their ability to translate across preclinical species with potential to monitor peripheral neuropathy in humans.

- Applicant consortium: will contribute expertise in in biomarker candidate evaluation, or experience with particular biomarkers for peripheral neuropathy which may contribute to the assessment of sample sets. Biomarker candidates will be evaluated in rat, dog, and Non-Human Primates. Assays will need to be established if not commercially available, and have some level of fit-for-purpose validation conducted. In addition to the assessment of sensitivity, specificity will also be determined for biomarker candidates.

- Industry consortium: will contribute expertise in assay development and analytical fit-for-purpose validation for clinical and/or non-clinical use. Industry participants will also provide samples (e.g. plasma, serum, cerebral spinal fluid) from rat, dog, and non-human primate studies with toxicants known to induce peripheral neuropathy. These study samples will be anchored with histopathological assessment, and should include nerve morphometry on semi-thin sections, neuro muscular junction (NMJ) imaging on whole mount and lumbrical muscle sections, functional endpoints (e.g. nerve conduction), as well as surrogate markers of small fiber damage such as intra-epidermal fiber density (IEFD) and conreal nerve fiber density (CNFD).

Work package 4 – Data and Samples Management

The goal of this work package is to ensure and develop appropriate processes for data and samples management with respect to guidelines and laws, including:

- Identification and standardisation of diverse data sources: preclinical and clinical data coming from Industry and Public;
- Develop plans for data (Data Management Plan, Data Sharing Plan) as well as for samples (Samples Management Plan and Samples sharing plan);

- Integration of data into an appropriate support (database).

Work package 5 – Consortium Coordination and Communication

The goal of this work package is the overall project coordination and communication, including:

- Define work expectations of different work streams, deliverables, dates and activities and review progress regarding adherence to budget, timelines and quality;
- Ensure legal and contractual management;
- Ensure the set-up of joint governance structure;
- Ensure appropriate communication/dissemination within the consortium and with the external scientific community and the public;
- Develop and manage communication via web portal and other social media tools with a repository of key document;
- Quality assessment of documents;
- Ensure that key cross-functional partners are engaged;
- Define project interdependencies, stakeholders and risks;
- Ensure ethics management.

References

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