Standard Operating Procedures

International Harmonization of Nomenclature and Diagnostic Criteria (INHAND)

Global Editorial Steering Committee

Version 2 Adopted January 2025

1. Purpose

This SOP outlines the responsibilities and procedures by which the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) Global Editorial and Steering Committee (GESC) functions. The primary charge of the INHAND GESC Committee is the oversight of a systematized terminology / nomenclature for non-proliferative and proliferative microscopic lesions in rodents (rats, mice) and non-rodents (dog, nonhuman primate, mini-pig, rabbit, and fish) as commonly used in toxicologic pathology. The GESC also advises the Standard for Exchange of Nonclinical Data (SEND) of the U.S. Food and Drug Administration (FDA) on microscopic pathology terms via the Controlled Terminology Working Group of the Clinical Data Interchange Standards Consortium (CDISC).

The GESC accomplishes much of its work via Working Groups organized to address an organ system, species, or other area requiring specialized terminology. The general organization of the GESC and Working Groups is provided in Figure 1.

The GESC is a collaborative effort of multiple global toxicologic pathology societies with the Society of Toxicologic Pathology (STP), European Society of Toxicologic Pathology (ESTP), British Society of Toxicologic Pathology (BSTP), and Japanese Society of Toxicologic Pathology (JSTP) being the founding and sustaining members. The STP provides administrative infrastructure.

2. GESC Responsibilities

The Committee's primary responsibility is the establishment and maintenance of a standardized terminology / nomenclature for non-proliferative and proliferative microscopic lesions in

- rodents (primary focus on rat and mouse)
- non-rodent species used in nonclinical safety assessment studies (focus on dog, nonhuman primate, mini-pig, rabbit, and fish)
- specialized areas of toxicologic pathology (e.g., ocular toxicologic pathology)

The GESC is a standing committee with the following tasks:

- Establishment of Working Groups (WG) including selection of WG chair and co-chairs and approval of any members.
- Define a common format for the INHAND term descriptions for terminology that is adopted for use on goRENI and in publications (See Appendix A).
- Review the draft terminology (including the individual INHAND term descriptions) that is developed by INHAND WGs prior to general membership review and/or publication.
- Involve the leadership and membership of the founding Societies (BSTP, ESTP, JSTP, and STP) in the review of the proposed terminology.
- Approve all INHAND publications, which will be targeted to journals focused on toxicologic pathology.
- Ensure updated information on terminology is provided on goRENI and provide this information to each Society.
- Review, provide feedback on, and approve or reject INHAND microscopic description change control requests.
- Select GESC members to serve as advisors concerning microscopic pathology terminology for the Standard for Exchange of Nonclinical Data (SEND) Controlled Terminology WG under CDISC organization.

- Conduct business on a regular basis via email, video or conference calls, and/or a face-to-face meeting during annual meetings of one or more sponsoring Societies. Meetings will be scheduled by the GESC Chair as needed.
- Coordinate with other Society committees regarding shared activities and interests.
- Communicate regularly with the leadership of the sponsoring Societies.

3. GESC Membership and Roles

The Committee will consist of the following:

- Chair
- Vice-Chair (Chair-elect)
- Members
- goRENI Representative
- Observers

Note: 5-year terms of service are recommended for INHAND GESC roles due the complexity and breadth of work of INHAND and the need to maintain consistency in approaches to toxicologic pathology terminology.

Chair

- Term of Service: The Chair will serve at least a 5-year term. The GESC may extend the term of a Chair at its discretion.
- Selection: The Vice-chair will assume the role of chair when the current chair completes their term of service or when otherwise directed by the GESC (see below for Vice-chair selection).
- Roles and Responsibilities
  - Provide leadership, guidance, and direction to the committee.
  - Will establish the meeting schedule, prepare the meeting agenda, and chair GESC meetings.
  - Provide sponsoring societies with an annual written report of INHAND activities for the prior year and other reports as requested. This report will include any anticipated project publication needs.
  - Provide an annual budget projection to the sponsoring societies including estimated costs. Publication cost estimates are not required.
  - Provide orientation and training for new members.
  - Form ad-hoc subcommittees of GESC members for specific tasks.
  - With consultation of full GESC either serve as, or appoint other GESC members, to serve as representatives to SEND CT WG (See SEND Representative Roles Below).

Vice-chair (also Chair-elect)

- Term of Service: The Vice-chair will serve at least a 5-year term. The GESC may extend the term of a Vice-chair at its discretion.
- Selection: The Vice-chair will be selected by the GESC membership and may come from any of the founding societies. In the event none of the current membership of GESC is willing to assume the role of Vice-chair, GESC members will work with their respective society to identify potential nominees for the vice-chair role.
- Roles and Responsibilities
  - Assist the Chair in developing meeting agendas.
  - Prepare draft minutes of GESC meetings.
  - Conduct yearly review of GESC and Working Group rosters to confirm membership.
  - Assist with other GESC activities as directed by the chair.

Members-at-large

- Scope (or Definition): Each founding society (BSTP, ESTP, JSTP, and STP) will select 2-3 representatives to serve as GESC members. The role of Chair does not count against the 3-representative limit. For example, the society that the chair originates from may still have 3 at-large members.
- Term of service: At the discretion of the sponsoring society with an expectation that members will serve at least a 5-year term.
- Roles and Responsibilities
  - Assist the committee with its general responsibilities.
  - As directed by the Chair serve as a liaison to working groups.
  - Have full voting rights in any matters that require a vote.
  - Communicate views and comments of the sponsoring societies to the GESC.
  - Communicate notable updates to their sponsoring society and work with the society to ensure any INHAND information on societies websites is updated.

goRENI Representative

- Scope: An individual selected by the Fraunhofer Institute or other organization or their qualified designee that is responsible for the goRENI database and website design, maintenance and operation.
- Term of Service: To be determined by the Fraunhofer Institute or other organization or qualified designee with an understanding of the complexity of the role and database
- Role and Responsibilities:
  - Provide subject matter expertise related to goRENI for database development and maintenance as well as end user interface
  - Together with the Chair manage contracts and finances related to goRENI
  - Have full voting rights in any matters that require a vote
  - Provide guidance to the GESC on the structure and hierarchy of standardized nomenclature
  - Manage goRENI.org website access including new member applications

Observers from Other Societies

- At their discretion the GESC may accept requests from societies or other organizations that wish to have an observer role on the GESC.
- Attend and participate in committee meetings and teleconferences at the discretion of the observer
- Receive copies of GESC agendas, minutes, and reports
- Bring INHAND questions and concerns to the GESC, as appropriate
- Communicate concerns, decisions or assigned duties from supporting societies to the GESC

SEND CT Representatives

- Representatives will be GESC members as appointed by the chair with GESC consultation
- Attend SEND Controlled Terminology meetings and provide feedback on proposed new terms and definitions; frequency is generally twice monthly but may vary based on committee workload
- Manage submission of new terminology or change control requests for new terms and/or modification to SEND based on INHAND updates and publications.

4. Working Groups

INHAND Working Groups (WG) consist of toxicologic pathologists with specific expertise in an organ system, species, or specialty area of toxicologic pathology pertinent to that working group. WG nominees may be recommended by a WG chair or a society, but WG membership will be approved by the GESC. The GESC will provide oversight to ensure geographic diversity and relevant subject matter expertise within each WG and will determine establishment of new working groups in collaboration with founding/sustaining Societies. Each WG will be led by a chair nominated and approved by the GESC and will have a GESC member appointed in a liaison role.

Process for Establishment of a Working Group and Constituent WG Membership

- GESC will approve the formation of any new Working Group
- Chairs of the WG will be selected by the GESC
- Members to the WG can be suggested by the societies, WG chair, GESC members, or by self-nomination by a toxicologic pathologist. The GESC will approve WG members.
- GESC will work to ensure diversity of geographic representation while engaging appropriate subject matter expertise on the WG and considering development of emerging talent and expertise as well as succession planning for the WG. Examples of appropriate qualifications for WG members include:
    - subject matter expertise as demonstrated by scientific publications
    - presentations at scientific meetings, or membership on relevant expert groups.
    - demonstrated ability to be an active and collaborative contributor.
    - relevant experience as supported by GESC or WG chair recommendation.
- There is no established length of service for WG chairs/members. WG chairs or members may be replaced as the GESC deems appropriate.
- Some WGs may warrant the inclusion of a co-chair to assist with the leadership of the group and provide for succession planning. WG chairs can recommend a co-chair; however, the GESC will make the final determination and either approve or reject potential co-chairs.

Role and Responsibilities of the Working Group Chair

- Organizes the working group including scheduling meetings
- Assigns tasks to members, e.g., responsibilities for specific terms, organs, or species
- Coordinates the flow of information between any sub-groups of the WG
- Manages timelines for completion of any products such as publications, change control documents, or updated INHAND term descriptions.
- Ensures high quality development, review, editing, and publishing of working group recommendations.
- Serves as expert and facilitator for questions from the GESC concerning terminology in SEND; convenes working group members as needed for discussion (e.g. change control request under the WG area of expertise)
- Lead periodic reassessment of terminology as directed by GESC

Role and Responsibilities of a Working Group Members

- Draft and/or revise INHAND term descriptions, including references and commentary, as assigned by WG chair
- Participate in WG discussion/review/approval of nomenclature recommendations
- Provide images to illustrate all lesions if feasible.
- Review and revise nomenclature, definitions, diagnostic criteria, and images for specific topics as directed by the GESC.

5. Change Control

- The GESC will establish processes to allow for additions, deletions, or revision of INHAND terminology.
- The change control process and documents will reside on the goRENI site.
- The GESC will ensure that INHAND nomenclature changes completed via the established process are subsequently presented to the SEND CT committee in order to ensure continued integration of INHAND and SEND for microscopic descriptions for toxicologic pathology and nonclinical safety

assessment

6. INHAND Education and Communication

- The GESC will strive to keep the toxicology, regulatory and toxicologic pathology communities informed and updated on matters related to standardized nonclinical microscopic terminology using any appropriate methods of communication including but not limited to the following
    i. Posters or oral presentations at toxicology, regulatory and/or toxicologic pathology conferences, symposia, and continuing education courses
    ii. Webinars
    iii. Publications
    iv. Scientific society newsletter updates
- For INHAND publications for which the GESC deems a notable or substantial change to the diagnostic terminology for an organ system or species is to be made and that full member review is warranted the following procedures apply:
    i. Following review/approval by the appropriate WG, the GESC will review the publication providing the revised microscopic terminology. The GESC chair will determine the review period but would typically provide a minimum of 2 weeks for GESC review.
    ii. Following GESC review, the WG will revise as needed and provide updated text and images for posting in goRENI.
    iii. In cases where full membership review is warranted, each society will send an email to their members indicating that members have 30 days (or longer if deemed necessary by GESC) to provide comments.
    iv. Following the member review, the WG will address comments as appropriate and provide GESC a revised version for review and approval. The GESC chair will determine the scope and duration of the review based on the extent and nature of the public comments.
    v. Following GESC approval, the WG chair will proceed with publication and coordinate with goRENI to finalize content.

7. GESC Reports

- The GESC shall produce an Annual Report each year that can be provided to each participating society.
- The annual report should include committee membership, a summary of committee accomplishments, issues/concerns (if any), future goals/plans, and any action items for sponsoring societies.

8. Budget

INHAND

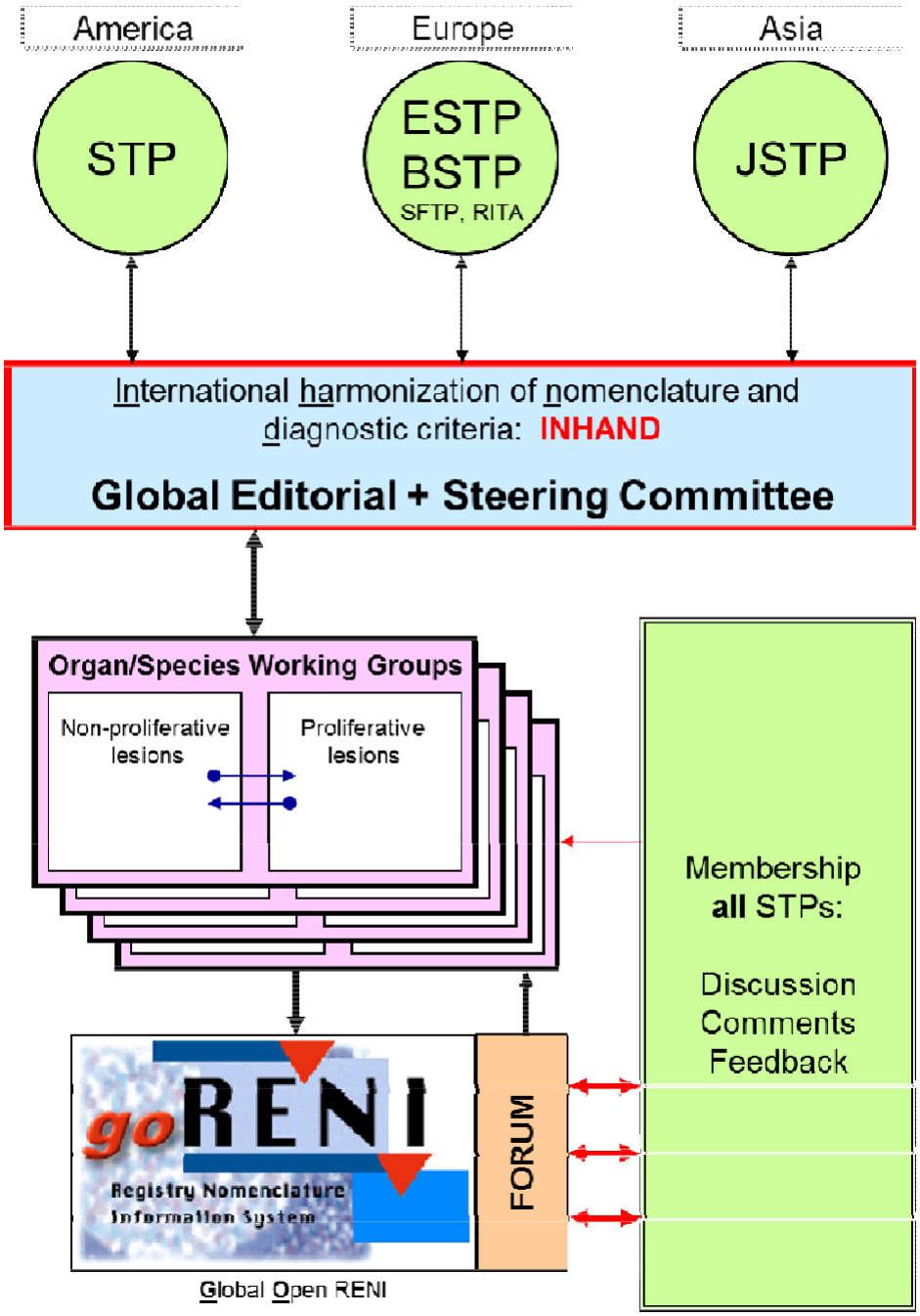
- GESC INHAND Committee budget requests are due to the STP Executive Committe on May 1st for the following year for operational committee expenses (e.g. AIM administrative support, meeting rooms at conference venue)
- This information is provided to the sponsoring societies to facilitate funding for INHAND activities
- If additional expenses arise that exceed the approved budget, the GESC may request additional funds with justification and may be made to one or more of the sponsoring societies.
- Budgets should project publications for the following year, but detailed costs for each publication are not required.

goRENI

- Support for goRENI.org website and data is provided via a contract with the Fraunhofer organization
- The contract between GESC, with signatures from each of the four founding/sustaining Societies (JSTP, ESTP, BSTP, STP) is valid for three years and renewed in the second half of the final year of the contract (e.g. in fall of 2024 for the contract for January 2025 to December of 2027).
- The Budget should account for expected manuscripts encompassing new working or ongoing working groups, estimated change controls and administrative tasks associated with new membership and should reflect discussion between the GESC committee chair and vice-chair and the goRENI representative to assess an accurate and fair budget for planned activities.
- Collaboration, discussion and approval by the participating societies who share the cost of the contract proportionally to society membership population size is undertaken by the GESC chair and vice chair in

consultation with GESC members at large for the participating societies and the Society leadership teams in a timely manner to ensure contract finalization prior to the end of the calendar year.

Figure 1



Organization of GESC and Working Groups

Appendix A

Definition and Structure of a "INHAND Term Description"

Within the INHAND nomenclature system, an INHAND term description describes the microscopic criteria for **one** lesion, which may occur in one or more than one organ. Differences in microscopic criteria among species should be mentioned in the text.

An INHAND term description consists of the following sections. Each of these sections can occur only **once** within a description. Within a section, sub-headers may be used for e.g. species or modifiers, if diagnostic criteria differ among them. While the OWG shall determine the appropriate level of detail for each entity, the overall concept for the documents are concise descriptions of diagnostic entities that allow ready use by toxicologic pathologists. References are used to refer the reader to more in depth discussion of the entity.

Organ name(s) [mandatory]

At least one organ must be assigned here. More organs may be mentioned if a particular lesion occurs in more than one organ. If a lesion can be diagnosed practically in all organs, the location should be defined as

- Soft tissue
- Musculo-Skeletal system
- Peripheral nervous system
- Vascular system
- [Generally used preferred terms]

Names of organs should be given always in singular, also for paired organs. The lexicon contains the information whether an organ exists paired, but it is not mentioned in the name.

The organs listed here should include all organs, where one particular lesion can be found (e.g. amyloidosis is a systemic disease therefore the location should be defined as generally used preferred term). The lesion will then be listed under all these organs and can be easily reached via the organ or organ system selections in goRENI.

Lesion name [mandatory]

There are two configuration options in the web-based format goRENI, which allow individual users to see either one or the other variant. This affects alphabetical listing of terms and every occurrence of the names in the manuscript title and links to other manuscripts. For the printed publication the OWG should use the form in which the lesion is listed first eg carcinoma, hepatocellular.

The preferred term for the lesion. If applicable, this is available in two variants with type of lesion first or descriptive component first. For example either carcinoma, hepatocellular or hepatocellular carcinoma

Biological behavior of lesions is important in goRENI for the listing of lesions within one organ and appropriate icon selection. Lesions are listed according to these categories first and within one category in alphabetical order.

N: non-proliferative and non-preneoplastic proliferative lesion including reactive lymphoid hyperplasia

Other Terms Used is the heading in goRENI that providesa list of similar terminology and can assist in finding a certain lesion via the index. Sometimes, a lesion, although available, may be remembered by some pathologists under a different name. These could thus be directed to the right manuscript. All names used in the SSNDC guides and WHO/IARC fascicles should be included in this entity if not the preferred term.

As the lesion names, these other terms used should be available in two variants with type of lesion first or descriptive component first.

Any list of names used (in the literature) synonymous for this lesion. As with the preferred terms, these other terms used should be available in two variants to be easily found in the goRENI index.

The OWG should define if the use is obligatory or descriptive / facultative for a certain lesion.

List of modifiers, which can be used to sub-classify a lesion (e.g., according to a specific growth pattern or a distinct cell type). Criteria for using a modifier should be given in the section "Diagnostic Features" under sub- headings.

Microscopic Diagnostic Features [mandatory]

Bulleted list of essential diagnostic criteria to be used for a specific finding, including staining characteristics, size criteria or growth patterns.

For all neoplastic lesions it is recommended to give information on the following topics: localization, distribution, demarcation, compression, capsule, architecture, growth pattern, cells / nuclei, mitosis, size criteria, other (preferably in that order).

For non-neoplastic lesions localization, distribution, cells, other (preferably in that order).

Special Techniques for Diagnostics [optional]

If desired, additional diagnostic techniques that may be helpful in determining the diagnosis can be included. Emphasis should be placed on when these techniques are useful from entities in the differential diagnosis. Categories may include:

- Special stains, histochemistry
- Immunohistochemistry
- In Situ-Hybridization
- Electron microscopy
- Other special diagnostic methods

Differential Diagnoses [mandatory]

List of lesions with similarities to the currently described one. This list should be accompanied by the main criteria for differentiation that should be given in bulleted form (only differentiating diagnostic criteria need to be listed here). The list items should be connected by using OR or AND to advise users whether individual entries are indicative on their own or must occur in combination.

Comment [optional]

Any additional information regarding the description of the lesion which is not necessarily relevant for making a diagnosis.

This section should be structured by sub-headings, like

- Distinguishing macroscopic features
- Frequency of the lesion

  Usual natural occurrence of this lesion in control animals (separated by sex), given as "extremely rare", "rare", "frequent". Remarks on the age-related occurrence should be included also.
- Pathogenesis

- Induced lesions

  Further comments on the induction of this lesion, e.g. by naming substance classes.
- Regulatory issues / remarks

  Any remarks regarding regulatory guidelines which need to be considered in certain studies when diagnosing this lesion.

References

Literature should not be older than 15 years, except fundamental and important papers. The citation format should be identical to the existing INHAND term descriptions / lesion descriptions. If abstracts in PubMed are available, links will be included.

The citation format should be identical to the existing term / lesion descriptions, as a transformation to the format for the different journals (ToxPath or Jap J Path) can be easily done by a computer program. The references should be given for each individual manuscript / lesion. For printing in the journal, redundant information for a whole organ system can be removed and references placed at the end of the manuscript. For goRENI it is useful to have the references lesion specific.

Images

Categories:

- Gross lesions (naturally occurring lesions / induced lesions)
- Micro photographs (naturally occurring lesions / induced lesions)

Preferable data in the legend:

- Organ, lesion, modifier
- Spontaneous vs. induced (by ...[type of compound])
- Strain (breeder), sex, age, animal status
- Further description

Please fill out at least the following template:

- *Rat / Mouse*
- *Organ*
- *Lesion*
- *Modifiers [if applicable]*
- *Stain [e.g. H&E]*
- *Magnification [e.g. x20, object lens only]*

The following information should be supplied if available:

- *Sex: male / female*
- *Age with number of days*

- *Strain*
- *Animal status: scheduled death / killed moribund / died*

For goRENI the number of images is not restricted. For the printed publication the OWG should select a limited number of images for each entity.

TrimmingLinks to the trimming guides (if applicable) will be automatically inserted by the software (see http://reni.item.fraunhofer.de/reni/trimming)

The links are supplied in goRENI to conveniently reach the trimming information. This will not be used in the printed publication, but can be referred to in introductory comments.