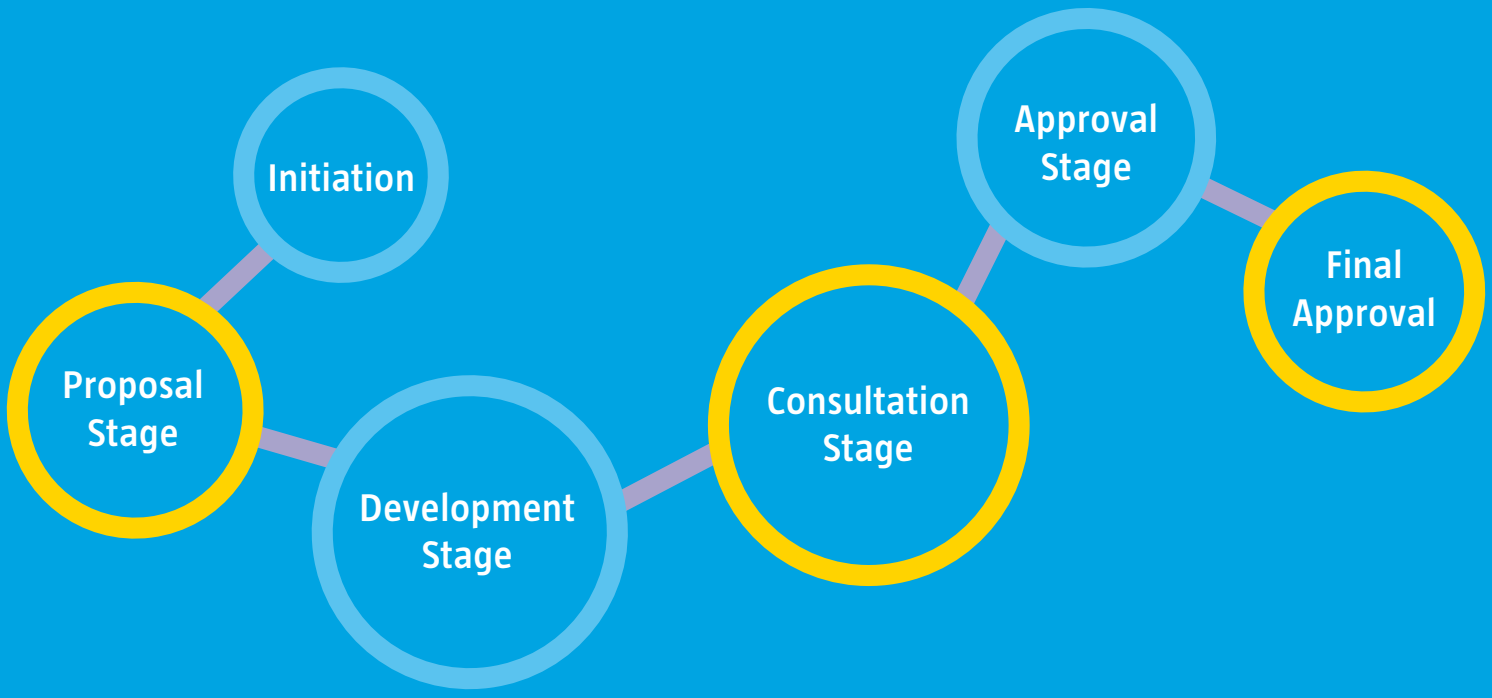
THE HUMAN VARIOME PROJECT

Standards Development Process



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Context

The Human Variome Project is an international consortium of scientists, doctors, informaticists and pathologists all working towards the complete capture and sharing of information on all human genetic variation effecting human disease.

The Human Variome Project Consortium envisions a world where the availability of and access to genetic variation information is not an impediment to diagnosis and treatment; where the burden of genetic disease on the human population is significantly decreased; and where the sharing of genetic variation information is standard clinical practice.
To facilitate the worldwide collection and sharing of all genetic variations, the Human Variome Project was created to establish and maintain the required standards, systems and infrastructure. This document outlines the process through which Human Variome Project Standards and Guidelines are produced.

What are HVP Standards and Guidelines

The Human Variome Project produces two categories of recommendations: HVP Standards and HVP Guidelines. HVP Standards are those systems, procedures and technologies that the Human Variome Project Consortium has determined shall be used by the community. These carry more weight than the less prescriptive HVP Guidelines, which cover those systems, procedures and technologies that the Human Variome Project Consortium has determined would be beneficial for the community to adopt.
From time to time, the International Scientific Advisory Committee may issue an HVP Recommendation to provide interim guidance on recommended technologies and practices while a formal HVP Standard
or Guideline undergoes development.
HVP Standards and Guidelines are central to supporting the work of the Human Variome Project Consortium and cover a wide range of fields and disciplines, from ethics to nomenclature, data transfer protocols to collection protocols for clinical data. They can be thought of as both technical manuals
and scientific documents, and while the impact of HVP Standards and Guidelines differ, they are both generated in a similar fashion.
HVP Standards and Guidelines make the collection, curation and sharing of information more efficient and reliable by establishing consistent protocols that can be universally understood. They facilitate interconnection of and interoperability between different systems.
HVP Standards and Guidelines represent a consensus of the Human Variome Project Consortium, each member of which has had the opportunity to participate in the development and review of each standard and guideline. In addition, as every effort is made to include all interests in the activity, HVP Standards and Guidelines can be considered to be representative of all interests concerned within the scope of each Standard or Guideline.
The Human Variome Project defines consensus as significant agreement between all affected parties covered by the scope of the standard or guideline. Consensus requires that all views and objections be considered, and that a concerted effort be made toward their resolution.

Project Oversight

The Human Variome Project takes its role of developing standards and guidelines very seriously, and is guided in this process, as in all others, by the principles of openness, inclusion and consensus.

The Human Variome Project is overseen by the Board of Directors of Human Variome Project International Limited, which is responsible for governance, policy development, strategic planning and financial sustainability.

The Board of Directors is advised by the International Scientific Advisory Committee in matters of strategic scientific direction for current and future projects. The Scientific Advisory has the delegated authority of the Board of Directors to publish all HVP Standards and Guidelines, and the arbitration of any dispute resolution processes in the generation of HVP Standards and Guidelines.

The International Scientific Advisory Committee consists of twelve members including one Chair. The International Scientific Advisory Committee members are elected by the two Advisory Councils every two years, with half the positions on the Committee becoming vacant every two years. The Chair of the International Scientific Advisory Committee is appointed by the Board from among the members of the Committee. Membership of the Committee, in an ex-officio capacity, is also extended to:

- the Scientific Director of the Human Variome Project Coordinating Office;
- the President of the Human Genome Variation Society;
- the President of the International Federation of Human Genetics Societies; and
- a representative from the central genetic databases, chosen from amongst themselves.

Any Individual Member of the Human Variome Project Consortium is eligible to stand for election to the International Scientific Advisory Committee. Candidates must be nominated and seconded by members of either of the Advisory Councils.

International Confederation of Countries Advisory Council

The International Confederation of Countries Advisory Council is composed of one representative from each of the HVP Country Nodes. Representatives are appointed by their respective Nodes; the Chair is elected by the membership of the Human Variome Project Consortium present at the HVP biennial meetings.

Gene/Disease Specific Database Advisory Council

The Gene/Disease Specific Database Advisory Council is composed of a representative from each gene/disease specific database recognised by the Human Variome Project. Representatives are appointed by the management of their respective databases; the Chair is elected by the membership of the Human Variome Project Consortium present at the HVP biennial meetings.

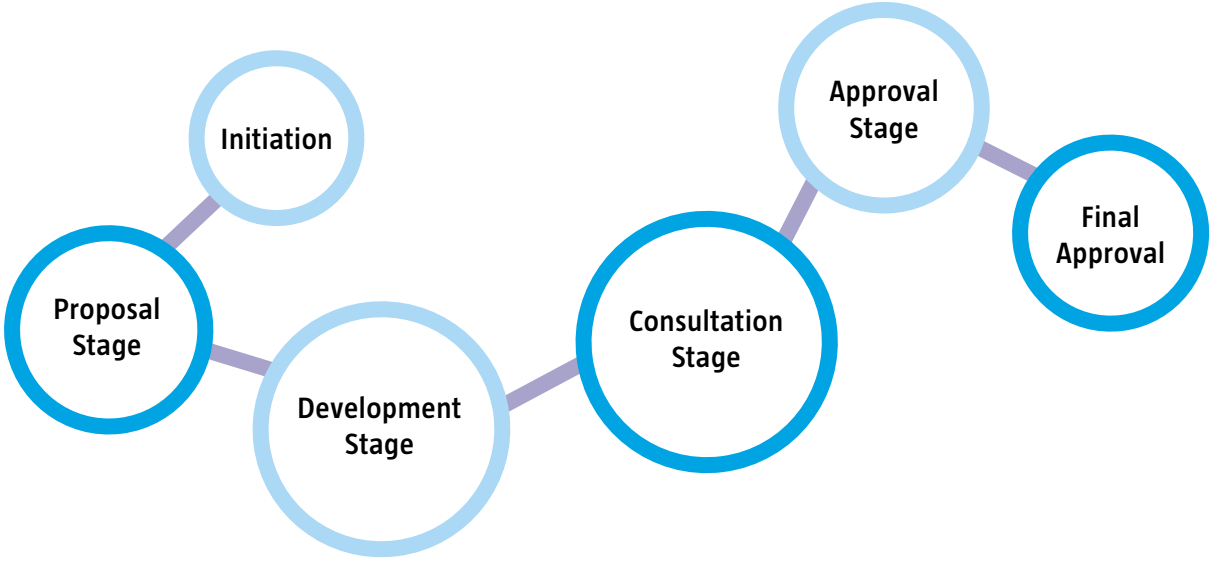
Standards Development Oversight

Ultimate oversight of the standards development process is provided by the Board of Directors. However, in practice, this authority is delegated by the Board to the International Scientific Advisory Committee. With this delegated authority, the International Scientific Advisory Committee has the power to authorise the publication of any draft standard or guideline recommended for publication by a Sponsoring Council—either the International Confederation of Countries Advisory Council for those standards

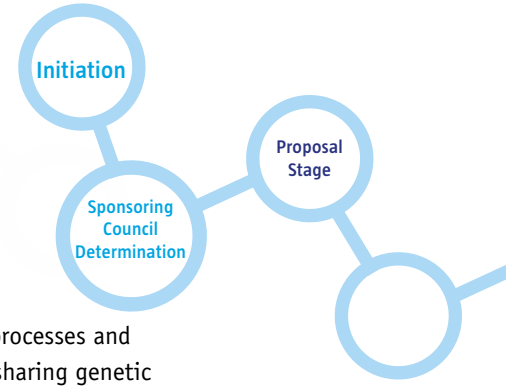
and guidelines pertaining to HVP Country Nodes, or the Gene/Disease Specific Database Advisory Council, for those standards and guidelines pertaining to gene/disease specific databases.
In cases where proposed standards and guidelines pertain to both HVP Country Nodes and gene/disease specific databases, the International Scientific Advisory Committee can act as the Sponsoring Council.

Process Summary

The process of developing a new standard or guideline is triggered whenever a Consortium member submits a request to develop a standard or guideline to the International Scientific Advisory Committee for review. The International Scientific Advisory Committee receives the request through the International Coordinating Office and refers it to the appropriate Sponsoring Council for review. A Human Variome Project Consortium Representative Body may also decide to initiate the process of developing a new standard or guideline in response to a request by one of its members.
Once the Sponsoring Council determines that the request should be granted, it instructs the International Coordinating Office to work with the requesting Consortium Member to recruit a volunteer Working Group to develop the draft standard. Working Group members can be any individual who has the necessary expertise or experience to make a substantial contribution to the draft standard. They do not need to be a member of the Human Variome Project Consortium, although this is encouraged. Terms of reference for each Working Group are established by the Sponsoring Council.
Working Groups are free to set their own organisation and meeting structure, but must regularly report their progress to the Sponsoring Council. The role of the Working Group is to achieve consensus on the content of the required standard or guideline and to develop the exposure draft that can be released for comment to the Consortium membership. This process may involve the authoring of multiple versions of the draft standard.
The exposure draft undergoes a period of public comment during which members of the Human Variome Project Consortium can voice their opinions on the content of the draft standard. All comments are referred back to the Working Group who must incorporate them in the final draft standard.
Once consensus amongst the Working Group has been achieved on the final draft standard, the Working Group Chair forwards it to the Sponsoring Council for consideration. The Sponsoring Council votes on the final draft standard and, when approved, recommends publication of the standard or guideline to the International Scientific Advisory Committee. The International Scientific Advisory Committee then decides to publish the standard or guideline, or refer it back to the Sponsoring Council for further refinement.



Standards Development Stages



INITIATION

The standards development process can be initiated by any Human Variome Project Consortium Member who recognises the need for a new standard or guideline, or believes that an existing standard or guideline needs to be updated in light of process or technological advances. HVP Standards and Guidelines are technical documents that outline best practice techniques, processes and technologies that must or should be used when storing, manipulating and sharing genetic variation data. Any standard or guideline can be superseded by a new standard or guideline at any point in its lifetime.

Requests to initiate the process are made to the International Scientific Advisory Committee by submitting an Activity Proposal (AP) through the International Coordinating Office.

An AP is a brief document that outlines the following:

- the need the proposed standard or guideline is attempting to address;
- the scope of the proposed activity;
- a plan of action for addressing the activity including suggested Working Group members;
- any resources required;
- the expected deliverables of the project; and
- a recommendation as to whether the final document should be considered for publication as an HVP Standard or HVP Guideline.

The International Coordinating Office comments on all APs to the International Scientific Advisory Committee with a particular view to identifying potential Working Group members and the capacity of the Human Variome Project to help secure the required resources.

Sponsoring Council Determination

Upon receipt of an AP, the International Scientific Advisory Committee makes a determination on which of the two Advisory Councils would be best placed to manage the standards development process going forward based on the scope of the proposed standard or guideline. In cases where the proposed standard or guideline pertains to both HVP Country Nodes and gene/disease specific databases, the International Scientific Advisory Committee may elect to act as the Sponsoring Council.

Once the International Scientific Advisory Committee has made a determination as to the appropriate Sponsoring Council, the AP is referred to the Sponsoring Council for approval. At this stage, a member of staff of the International Coordinating Office is appointed to be the liaison officer for the duration of the development process.

Sponsoring Council Initiated Activities

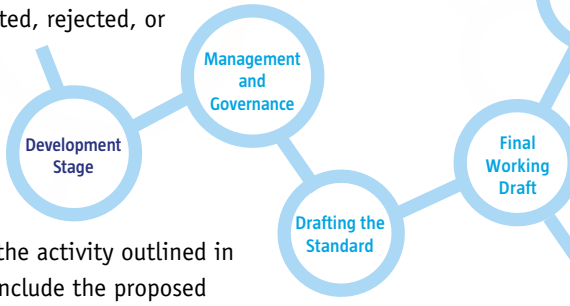
Representatives of HVP Country Nodes and Gene/Disease Specific Databases that have a seat on the relevant Advisory Council, as well as members of the International Scientific Advisory Committee, can request that their Council or Committee initiate the Standards Development Process directly without a formal Activity Proposal or ISAC Determination.

PROPOSAL STAGE

Once received by the Sponsoring Council, the AP is placed on the agenda for the next meeting of the Sponsoring Council by the liaison officer. Members of the Sponsoring Council are asked to review all APs and submit any comments they may have on the proposal prior to the meeting.

At the next meeting of the Sponsoring Council the AP is either accepted, rejected, or referred back to the submitter for clarification and refinement. A simple majority of a properly constituted meeting of the Sponsoring Council is all that is required to approve an AP.

If the AP is accepted, or the Sponsoring Council decides to initiate activity at the request of a member, at that same meeting, the Sponsoring Council must charter a new Working Group to undertake the activity outlined in the proposal, or modify the charter of an existing Working Group to include the proposed activity.



DEVELOPMENT STAGE

HVP Working Groups are subcommittees of their Sponsoring Council that have been convened for the purpose of developing a single standard or guideline. Membership of any Working Group is open to any Consortium Member who believes he/she can make a substantial contribution to the standard or guideline under development. Individuals who are not Human Variome Project Consortium members can be invited to join a Working Group by the Working Group Chair or the Chair of the Sponsoring Council. The Sponsoring Council must make every effort to ensure that a diverse range of opinions and expertises are represented on the Working Group.

Upon chartering a Working Group, the Sponsoring Council must invite initial members to take part. These are generally the individuals listed in the AP, but the Sponsoring Council can make an invitation to any person they think fit. The Sponsoring Council must also appoint a Chair of the Working Group at this time.

All active Working Groups are listed on the Human Variome Project website along with a repository of their meeting agendas and outcomes and the contact details of all members. The Human Variome Project website also provides a dedicated space restricted to Working Group members where they can discuss their work, collaborate on drafts and cast votes to settle disputes etc.

Once chartered, a Working Group has a maximum of two years to complete the Development Stage of the standards development process. The Working Group must submit a written report to the Chair of the Sponsoring Council at every meeting of the Sponsoring Council for which the Working Group is constituted.

Management and Governance

Working Groups collaborate to prepare a draft of the standard or guideline specified in their charter. They are free to set their own meeting schedule and will be provided assistance to conduct teleconferences and online discussion by the International Coordinating Office. Requests to assist with funding Working Group members to attend face-to-face meetings may be considered on a case-by-case basis by the International Coordinating Office, although the resources to do so are very limited.

The Sponsoring Council is responsible for the management of every Working Groups it charters. It is assisted by the International Coordinating Office in this process. Working Groups are encouraged to resolve any impasses or disputes internally, but if this is not possible, the

Sponsoring Council can be requested to adjudicate. Any Working Group member can raise an issue for adjudication through the liaison officer appointed by the International Coordinating Office.

It is the responsibility of the Working Group Chair to drive the activity of the Working Group by organising meetings, setting goals and monitoring progress. The Chair may set whatever meeting schedule they deem appropriate, but all Working Group members must be informed in writing of a meeting with at least two weeks notice. The liaison officer appointed by the International Coordinating Office should be included in all communications.

Working Groups must abide by the Human Variome Project principles of openness, inclusion and consensus. It is the Chair's responsibility to ensure that all points of view are considered when drafting a standard and that consensus is reached.

Drafting the Standard

All Working Groups should strive to have a complete Working Draft (WD) of their standard complete within the shortest possible time frame. Working Groups must complete the Development Stage of the standards development process within two years or they run the risk of their Sponsoring Council disbanding the entire group. To assist in this process, each Working Group must submit a detailed outline and schedule of work for their standard or guideline to their Sponsoring Council within three months of being chartered.

How the physical task of writing up the WD is conducted will differ between Working Groups and should be undertaken in whatever manner makes the most sense for each group. The most advisable process would be to use Working Group meetings as forums for the discussion of content and a way of making substantive decisions about what to include in the written document, rather than a collaborative writing session. Writing tasks can then be divided up among members to make the most efficient use of everyone's time.

Standards and Guidelines are intended to be comprehensive technical documents that describe best practice processes and technology. They should be sufficiently detailed to allow any individual to implement the described best practice with a minimum of background knowledge on the subject and without the need to refer to large numbers of external sources.

The Development Stage of the standards development process is meant to be an iterative process and as such it is anticipated that each Working Group will prepare multiple WDs as ideas mature and consensus amongst the group is obtained. Beyond ensuring that a copy of each WD is lodged with the International Coordinating Office once finalised, Working Groups are able to move from version to version at the discretion of the Chair.

Working Groups must ensure that every version of the WD contains the necessary copyright notice that is specified from time to time by the International Scientific Advisory Committee.

Final Working Draft

When the Chair of the Working Group is satisfied that the current WD represents a consensus view of the entire Working Group, they can initiate a vote to recommend the WD to the Sponsoring Council as an Exposure Draft (ED). Voting is open to all members of the Working Group and requires a supermajority of 75% of Working Group members to approve recommendation as an ED.

The voting process lasts for seven days and is managed by the liaison officer appointed by the International Coordinating Office. Each Working Group member can cast a single vote to approve

recommendation, disapprove of recommendation or abstain from the vote.
If recommendation is not approved, the Working Group must start work on a new WD version in which they address the problems raised during the vote. A failed vote does not confer any more time on the Working Group to complete the Development Stage, so it is advisable for the Chair to ensure consensus is reached well before the two year time limit. A Sponsoring Council may agree to extend the lifespan of a Working Group beyond the initial two years if they feel that consensus is in sight of being reached.
There is no limit to the number of times a Working Group can vote to recommend a WD as an ED, but each vote must be on a new WD version. A single WD version cannot be voted on more than once.

CONSULTATION STAGE

Editing

Upon the successful completion of the Development Stage, the final WD is handed over to the International Coordinating Office to be edited for style, grammar, concision and clarity—it is important to note that this is not a process of technical editing. The International Coordinating Officer staff member performing the edit will work closely with the Working Group Chair to ensure that the ED presented to the Sponsoring Council is of the highest quality.

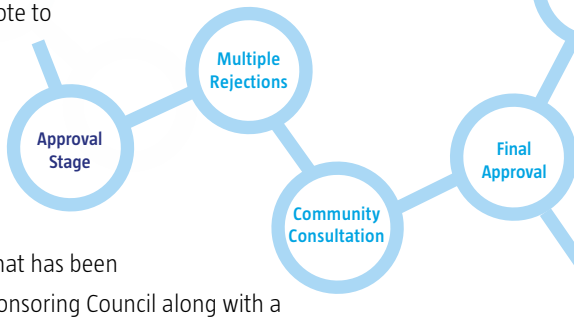
Community Consultation

Once the edited ED has been accepted by the Working Group Chair, it is released for comment to the Human Variome Project Consortium membership via the Human Variome Project website.
The consultation period will last for a period of sixty days, but can be extended at the request of the Sponsoring Council or the Working Group Chair.
Consortium Members will be invited to provide feedback on the ED in writing via the Human Variome Project website. Members submitting comments on the ED will be asked to indicate whether the ED should be accepted without revision, accepted with minor revisions, or not accepted for publication.
If at least 50% of Consortium members providing comments on the ED recommend acceptance with or without minor revisions, the ED will be deemed acceptable by the community. The next step in the process is for the draft standard to be approved by the Sponsoring Council at their next meeting. However, before being handed to the Sponsoring Council for approval, the Working Group must perform any required minor revisions and prepare a written response to the comments received. Working Groups have sixty days in which to respond to the comments and submit the revised ED to the Sponsoring Council for approval.
In some cases, where the Working Group Chair decides that the comments raised by those members not recommending acceptance for publication merit further work, the Chair may elect to voluntarily return the ED to the Development Stage for further revision.

Further Drafts

If less than 50% of the Consortium members providing comments on the ED do not recommend acceptance for publication, or the Working Group Chair voluntarily elects to do so, the ED will be returned to the Working Group to repeat the Development Stage and substantially revise the draft standard.

The original Working Group is retained to begin development on a new WD and will have a further period of six months to complete a WD that represents a consensus view of the Working Group.
Once the revisions have been completed the Working Group must again vote to recommend the WD to the Sponsoring Council as an Exposure Draft (ED) and, once recommended, the new ED must undergo a further Consultation Stage.



APPROVAL STAGE

The Approval Stage begins once the Working Group Chair submits an ED that has been recommended for acceptance for publication by the Consortium to the Sponsoring Council along with a detailed response to the comments raised during the consultation period. The International Coordinating Office will ensure that a vote on the ED is added to the agenda of the Sponsoring Council's next meeting. One month prior to the meeting, the International Coordinating Office will send to all members of the Sponsoring Council a copy of the draft standard or guideline, a summary of the comments received during the Consultation Stage and the Working Group's response to the comments.
A supermajority of 75% of all members of the Sponsoring Council voting on the matter is required to accept the draft standard or guideline for publication. Sponsoring Council members can vote to approve or disapprove of publication, or abstain from voting. Members have the right to have a comment attached to their vote recorded in the minutes, but this is not required.
Draft standards and guidelines not approved for publication will be returned to the Development Stage where the existing Working Group will have a further six months to produce a new ED for community consultation.
Draft standards and guidelines approved for publication by the Sponsoring Council will move to the Final Approval Stage, along with a recommendation from the Sponsoring Council on whether the draft should be published as an HVP Standard or an HVP Guideline.

Multiple Rejections

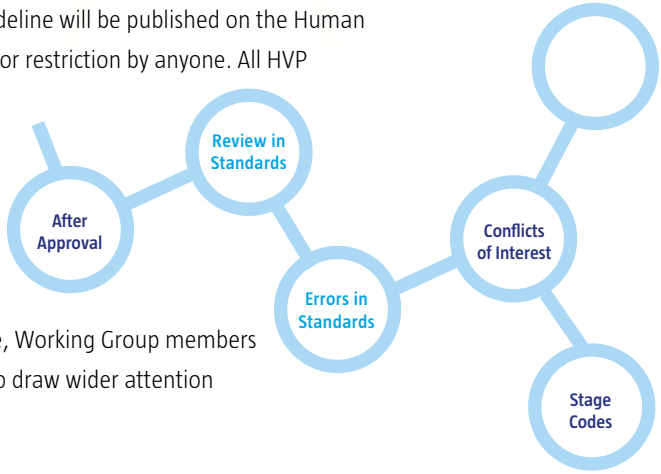
If the Sponsoring Council fails to approve a draft standard or guideline for publication three times, the Sponsoring Council will be forced to declare the project non-viable and abandon the standards development process. The process may be reinitiated from the beginning at any time.

FINAL APPROVAL

Approval for publication by the Sponsoring Council does not guarantee a draft standard or guideline will be published. Final approval must first be obtained from the International Scientific Advisory Committee. A simple majority is all that is required to grant final approval to publish the draft. At the same time, the International Scientific Advisory Committee will make a determination on whether to publish the draft as an HVP Standard or an HVP Guideline.
If final approval is not obtained from the International Scientific Advisory Committee, the Sponsoring Council must either refer the draft back to the Working Group for further refinement during a further six month long Development Stage, or abandon the project entirely.

After Approval

Once final approval has been achieved, the HVP Standard or Guideline will be published on the Human Variome Project website where it can be accessed free of charge or restriction by anyone. All HVP Standards and Guidelines are published with the Working Group as the designated author and copyright assigned to Human Variome Project International Ltd. All Working Group Members are listed and acknowledged in the text of the published document. As technical documents HVP Standards and Guidelines are generally not suitable for publication in most academic journals; however, once published on the HVP Website, Working Group members may wish to consider writing an article for an academic journal to draw wider attention to the presence of the HVP Standard or Guideline.



Review of standards

HVP Standards and Guidelines are enduring documents and do not have a defined life. However, they are expected to be reviewed and updated or superseded as new technologies and processes are developed. Any HVP Standard or Guideline can be reviewed at the request of a Consortium member after 2 years have elapsed from the date of publication. Such a request would initiate the standards development process in an identical fashion to if a new standard had been requested—the only change being the Working Group would be charted to review and update the existing standard rather than develop a new one.

Errors in Standards

Errors in published HVP Standards and Guidelines that are discovered prior to the two years after publication milestone are addressed by the Working Group Chair or their nominee issuing an Erratum that will be published alongside the HVP Standard or Guideline. All members of the Working Group are encouraged to contribute to the Erratum.

Errata do not need to undergo the Consultation Stage of the standards development process, but must be approved for publication by the Sponsoring Council and the International Scientific Advisory Committee. The Working Group Chair or their nominee may request an early review of the published HVP Standard or Guideline if they feel that publishing an Erratum is not the best method of dealing with the identified error.

Conflicts of Interest

Individuals wanting to participate in a Working Group must declare any potential conflicts of interest to the Sponsoring Council.

Stage Codes

The stage at which a particular draft standard is at in the standards development process can be identified using the following Stage Codes.

STAGE CODES	10 Registration	20 Preparatory	50 Main Activity	80 Main Activity	91 Repeat Earlier	92 Repeat Current	98 Abandon	99 Proceed
00 Initiation	AP Received by ICO	ICO forwards AP with comments to ISAC	ISAC determines which body will act as SC	ISAC determination complete				AP referred to SC
10 Proposal	SC Registers AP	AP sent to all SC members	SC votes on AP	Voting complete	AP referred back to submitter for refinement		AP rejected	Working Group chartered
20 Development	Working Group convened	Outline and Schedule of Work submitted	First WD begun	WG vote to accept WD		Further WD required	WG disbanded	WD approved as ED
30 Consultation	ED registered by ICO	ED edited by ICO	Consulation Period begun	Consultation finished	WG to address issues raised during consultation			ED accepted
40 Approval	ED and WG response to comments received	Vote scheduled	SC vote to approve publication	Voting complete	WG to address issues raised by SC		Project abandoned	Draft approved for publication
50 Final Approval	ISAC receive approved draft	Vote scheduled	ISAC vote to give final approval	Voting complete	Draft returned to SC for decision			Draft has obtained final approval
60 Publication	HVP Standard or Guideline published on HVP website							

ABBREVIATIONS

AP – Activity Proposal
ED – Exposure Draft
HVP – Human Variome Project
ICO – International Coordinating Office
ISAC – International Scientific Advisory Committee
SC – Sponsoring Council
WD – Working Draft
WG – Working Group