

**Global Advisory Committee on Vaccine Safety (GACVS):
Sub-Committee on Novel OPV2 (nOPV2) - Terms of Reference**

Background

The type 2 novel oral poliovirus vaccine (nOPV2) is a modified version of the current Sabin OPV vaccine that provides comparable immunity against poliovirus whilst being more genetically stable. The vaccine has completed a phase I and two II trials in Belgium and Panama and found to be safe and immunogenic. Another Phase II trial has begun in newborn infants in Bangladesh and a Phase III trial will be launched in the Gambia in the coming months. The nOPV2 has been submitted for assessment under WHO's Emergency Use Listing (EUL), a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in vitro diagnostics for use primarily during public health emergencies of international concern (PHEIC).

Once EUL is authorized/recommended (authorization is anticipated towards the end of 2020), nOPV2 can be implemented in outbreak response mass vaccination campaigns (anticipated ~6-8 weeks after EUL authorization) for type 2 circulating vaccine derived poliovirus. The SAGE have endorsed that for the initial period of use (anticipated to last 3-6 months), nOPV2 is only used in countries that meet additional "initial use criteria" for enhanced surveillance including safety monitoring¹:

1. Additional surveillance and safety monitoring activities to meet the essential criteria for initial use
2. nOPV2 should be the only oral polio vaccine used in a geographic area where cVDPV2s are present and
3. The country in question has robust disease surveillance to ensure optimal analysis of the vaccine's performance.

The use of nOPV2 under EUL is expected to be ongoing until vaccine prequalification and licensure (anticipated to last ~18 months, until 2023). This will be the first time the WHO's EUL mechanism is used for a vaccine and as such safety monitoring is critical. The decision to transition from initial use to wider use under EUL (i.e. lifting the requirement to meet initial use criteria) will be informed by an independent analysis of safety outcomes, and SAGE recommended establishing the GACVS sub-committee on nOPV2 Safety for this purpose.

The GACVS sub-committee on nOPV2 Safety is a panel of independent expert members whose primary objective is to advise the clinical safety outcomes related to the use of nOPV2 under EUL, including: adverse Events Following Immunization (AEFI); Adverse Events of Special Interest (AESI); and Vaccine

¹ <http://polioeradication.org/wp-content/uploads/2020/10/Interim-Guidance-on-the-use-of-nOPV2-during-the-initial-use-period-20201022.pdf>

² Annex 1 overview organogram; Annex 2 Key groups - roles and responsibilities

Associated Paralytic Poliomyelitis (VAPP). The GACVS sub-committee on nOPV2 Safety will evaluate safety data and provide recommendations on nOPV2 use to the Global Polio Eradication Initiative².

Composition

The GACVS sub-committee on nOPV2 Safety will be presided by two co-chairs and consist of total 8 independent members, comprised of a mix of current GACVS members (including the Chair, Co-chair, and another GACVS member with polio experience), as well as additional members with Polio and nOPV2 specific expertise. Members will have expertise in but not limited to the following areas:

- Evaluation of vaccine safety and efficacy
- Biostatistics
- Programmatic implementation of vaccines
- Senior clinician
- Epidemiology
- Experience in Global Advisory Committee for Vaccine Safety
- Experience in DSMB

There will be due consideration to ensure gender balance and regional representation. Given that the majority of type 2 polio outbreaks are currently occurring in Africa, and the use of nOPV2 is expected to be highest in that region, members with expertise in and understanding of the African context will be actively sought.

Purpose of the GACVS Sub-Committee on nOPV2

The GACVS sub-committee on nOPV2 Safety will:

1. Review the current plan for safety data collection around use of nOPV2 under EUL and advise the nOPV2 WG of any gaps.
2. Review regular report/summary of safety data generated during use of nOPV2 over the entire period of EUL (these reports will be prepared by an external consultant on a monthly basis during the initial use period, then quarterly thereafter). These reports will include summarised and analysed data for:
 - a. Adverse Events Following Immunization (AEFI)
 - b. Adverse Events of Special Interest (AESI)
 - c. Vaccine Associated Paralytic Poliomyelitis (VAPP)
 - d. Safety outcomes involving high risk groups, including from the observational study of pregnant women and surveillance of individuals with primary immunodeficiency (where relevant)
 - e. Relevant documents such as causality assessments, medical reports, investigation forms (where relevant)
3. The outcomes involving evaluation of safety data related to the genetic stability of nOPV2 will be made available to the GACVS Sub-Committee on nOPV2. The GACVS sub-committee

on nOPV2 Safety may provide comment / query, however the scope of in-depth evaluation and assessment of the genetic data will be conducted by the already established nOPV2 Genetic Characterization Sub-Group.

4. Review aggregated data of serious adverse events, and meet on an emergency basis as is required (eg if there are clusters of severe adverse events)
5. Based on review of safety data (3-4) provide key recommendations to the nOPV2 WG and GACVS, in the following areas:
 - a. An independent assessment of safety after each nOPV2 campaign (approximately 12 weeks completion after each campaign, to allow sufficient time for surveillance, field investigation and data compilation) during the initial use period.
 - b. Recommendation when safety data is sufficient to support the transition from initial use to wider use of nOPV2 under EUL.
 - c. Once nOPV2 use is expanded beyond the initial use period, provide a quarterly report to nOPV2 WG of safety assessment.
 - d. Recommendation to discontinue nOPV2 use (temporarily or permanently) based on safety data.

Operations

Chair

The GACVS sub-committee on nOPV2 will be overseen by 2 co-chairs – a member from the full GACVS, and the other with polio specific expertise.

Secretariat

There will be a joint secretariat for the GACVS sub-committee on nOPV2 Safety based in WHO, with representation from WHO's Polio research and Pharmacovigilance teams. The Secretariat's role will be to provide technical and administrative support to ensure the sub-committee functions smoothly and delivers timely and effectively on its Terms of Reference. A contract will be issued by the secretariat to an external contractor to facilitate compilation and analyses of the safety data for onward sharing with the GACVS sub-committee; the contractor will also have access to the analyses of genetic stability data. The day-to-day coordination of the GACVS sub-Committee, including setting dates for meetings, and ensuring action items are followed up on, will be managed by POL.

Expected availability

It is anticipated that members of the GACVS sub-committee on nOPV2 Safety will be available for up to 4-6 person hrs per month, including convening at least once per month face-to-face or by teleconference, during the period December 2020 for a period of 6 months with likely extension to 18 months. The frequency and format of the meetings will be decided by WHO. Should the need arise, the GACVS sub-committee on nOPV2 Safety may request a meeting at any time with nOPV2 WG or full GACVS. Safety Advisory group members should endeavour as much as possible, to attend urgent /emergency meetings on short notice, should a serious safety concern be raised.

The recommendation to move from initial use of nOPV2 under EUL to wider use of nOPV2 under EUL, all GACVS would be conveyed by the sub-committee members to the nOPV2 WG and full GACVS. The nOPV2 WG will through the existing channels of communication will put the available supporting scientific evidence and recommendation forward to the SAGE Polio WG / SAGE.

Confidentiality

All information and documentation to which members may gain access in performing their GACVS sub-committee on nOPV2 Safety function will be considered as confidential and proprietary to WHO and in addition, to the GPEI and nOPV2 WG, as relevant. Members of the GACVS sub-committee on nOPV2 Safety shall not purport to speak on behalf of, or represent, WHO, GPEI, nOPV2 Working Group to any third party.

Conflict of interest

Members of the GACVS sub-committee on nOPV2 Safety should not have any involvement in the direct conduct of nOPV2 implementation, neither hold financial, proprietary, professional, organizational, or other interests which could potentially affect their impartial decision-making. Members should be willing to confirm this in writing, disclose any potential conflicts of interest, and sign a declaration of interest certification at the time of participation and prior to each meeting.

Specific meetings and deliverables

A tentative schedule of meetings is outlined below. All supporting documents and data to be reviewed by the GACVS sub-committee on nOPV2 Safety will be prepared in advance of the meetings, by an external consultant group on a monthly basis.

1. Initial meeting (1-2) to
 - a. Discuss terms of reference and review background documents including the methodological approaches to monitor nOPV2 safety such as protocols, timelines etc.
 - b. Establish safety considerations to i) recommend discontinuing nOPV2 use and ii) and to complement criteria used to recommend transition to wider use of nOPV2 under EUL.
2. Monthly review meetings during initial use period (approx. 3-6 months) to
 - a. Review monthly safety reports
 - b. Provide a formal report including recommendations based on the review of safety data, after each vaccination campaign (approximately 10 weeks completion after each campaign): the second report would also provide recommendations to address consolidated safety data from both vaccination campaigns. The GACVS sub-committee on nOPV2 Safety will be prepared in advance of the meetings, by an external consultant group on a monthly basis
3. Quarterly review meetings after initial use period (approx. 18 months from when EUL authorization is granted).

Documentation incorporating key analyses and the recommendations from the GACVS sub-committee on nOPV2 Safety will be synthesized into a formal report drafted by the external consultant, to be finalized by the GACVS sub-committee on nOPV2. The finalized report(s), will then be shared with the nOPV2 WG and full GACVS with a timely period, most likely within 14 day after reviewing relevant analyses. The final consolidated report will address the GACVS sub-committee on nOPV2's decision regarding transition from initial use to wider use of nOPV2 under EUL contingent on safety outcomes, and will be distributed to both the nOPV2 WG and presented to the full GACVS.

Implementation of recommendations

The GACVS sub-committee on nOPV2 Safety will provide their recommendation in a formal report through the Secretariats to the nOPV2 WG and the full GACVS. The nOPV2 WG will provide the nOPV2 Safety Advisory Committee's reports / recommendations to GPEI, SAGE Polio WG, SAGE, Biofarma and other groups as needed. Safety related updates relating to policy recommendations would be presented by the GACVS sub-committee on nOPV2 Safety to the nOPV2 WG Polio SAGE WG and as an agenda item to the SAGE. WHO retains full control over the publication of the reports of the sub-committee's meetings, including whether or not to publish them.

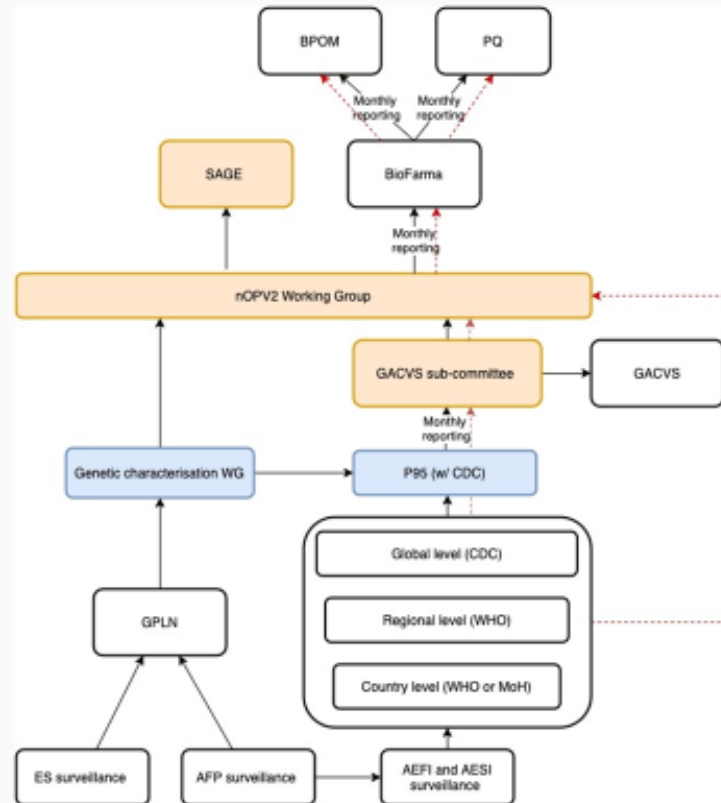
Annex 1 Overview Organogram

Data flow from country to global level

- General flow (may not always be sequential)
- Reporting of serious AEs
- Data analysis
- Data review and policy

*Data will go straight from country/regional to external consultant and CDC at same time

*Any reported serious adverse event should be immediately be made known to the GPEI and nOPV2 WG, to be reported to the manufacturer, for their onward reporting to both their national regulatory authority and WHO PQ within 14 days. (Focal point within nOPV2 WG: Martin Eisenhower)



Summary of roles and responsibilities:

AEI/AEFI country level /regional/global level: Data flow and mechanisms to differ between countries, depending on existing mechanisms. Data generated at country level and shared with regional/global level and external consultant group.

CDC: responsible for country training and implementation of AEFI/AESI safety surveillance, providing technical support to countries and tracking data flow up from field to the global level. For the initial use period, CDC will work with P95 to analyze AEFI/AESI safety data for reporting to the GACVS sub-committee.

Genetic characterization sub-group: Analyse nOPV-related AFP and ES genetic data from CDC and NIBSC laboratories. Reports of data to nOPV2 WG.

P95: Technical support the GACVS sub-committee. Maintain and analyze database of AEFI/AESI safety. Generate a monthly report of AEFI/AESI and combine with genetic stability (provided by the genetic stability subgroup) to go to GACVS subcommittee.

GACVS sub-committee on nOPV2 Safety: Provide an independent evaluation of AEFI/AESI data (genetic stability data provided for information) and recommendations on nOPV2 use to the nOPV2 WG. Focal point

nOPV2 WG:

1. Ongoing support/review/tracking of genetic stability and AEFI/AESI
2. Provide reports of safety to Biofarma – outlined in commitments under EUL post-deployment monitoring.
3. Provide policy recommendations to be endorsed by the SAGE Polio WG (to full SAGE) on GPEI use of nOPV2, consolidating recommendations from various bodies/committees and GPEI programme.

Polio SAGE WG/ full SAGE: Review and endorse policy on GPEI use of nOPV2 (that will be presented by nOPV2 WG).