

A consensus-based guideline for personalized bacteriophage therapy

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Bacteriophages (phages) – viruses that selectively infect bacteria – are a promising option for personalized therapy of difficult-to-treat bacterial infections. Clinical implementation in many countries worldwide, however, faces multiple hurdles, including a lack of consensus on general principles for phage therapy, infrastructural requirements, procedures for quality-assured phage selection and preparation, clinical administration, monitoring and documentation. Existing guidance provides limited practical direction across the entire translational pathway and lacks inspection-ready specifications to support both pharmacies and clinical sites. These gaps impede safe and transparent clinical use and effective regulatory oversight. Likewise, there are no established processes to identify research questions that will be key to advancing clinical phage research in the future. To address these needs, this consensus-based guideline was developed within the methodological framework of the Association of the Scientific Medical Societies in Germany under the leadership of the German Society for Infectious Diseases. It was created through a collaborative effort involving 20 professional societies, patient advocacy groups and regulatory authorities and 18 international experts. The guideline provides over 60 recommendations on core principles, infrastructure, preparation and quality control, administration and future research. Recommendations are supported by international societies, organizations and stakeholders. By providing clear and practice-oriented recommendations, this consensus statement paves the way for the safe and standardized use of personalized phage therapy.

The accelerating global crisis of antimicrobial resistance poses an existential threat to modern medicine, driving renewed interest in bacteriophage (phage) therapy as a targeted approach for the treatment of bacterial infections. Despite growing clinical use, often as a last-resort intervention, broader implementation of personalized phage therapy in many regions of the world remains constrained by the absence of clear, harmonized and practice-oriented guidance. This gap is becoming increasingly evident as physicians, pharmacists, patients and regulators seek structured pathways for integrating personalized phage therapy into clinical care when conventional antimicrobial options have failed.

This guideline aims to address this unmet need by providing practical, consensus-based recommendations for safe and effective

personalized phage therapy in Germany and beyond. It focuses on core principles underpinning phage therapy, infrastructural and organizational requirements, standards for phage preparation and quality control, clinical administration considerations and priorities for future translational and clinical research. This document seeks to translate foundational principles into actionable guidance applicable to real-world clinical settings.

The guideline was developed by an international and interdisciplinary group of experts. This collaboration integrated clinical expertise in infectious diseases, clinical microbiology and various medical specialties with technical knowledge in pharmacology, toxicology and biotechnology as well as regulatory and quality affairs. National and

international phage experts, as well as representatives from patient advocacy groups, were actively involved from an early stage to ensure inclusivity, relevance and alignment with clinical and societal needs. The final recommendations have been reviewed and supported by additional key international societies, organizations and stakeholders, underscoring their broad acceptance and applicability.

All recommendations were formulated using a structured, consensus-based methodology in accordance with the standards of the Association of the Scientific Medical Societies in Germany (AWMF) for consensus-based guidelines. Structured consensus techniques were applied under neutral moderation by AWMF representatives to ensure transparency, rigor and balance.

Given the biological, clinical and regulatory complexity of phage therapy, as well as the limited available evidence, this guideline does not aim to be exhaustive or to address every possible clinical scenario. Rather, it provides a structured framework to support clinicians, pharmacists, researchers and policymakers in navigating the key challenges of personalized phage therapy and advancing its responsible integration into contemporary medical practice.

Methodology

This consensus guideline was developed within the structured methodological framework of the AWMF under the leadership of the German Society for Infectious Diseases (Deutsche Gesellschaft für Infektiologie e.V. (DGI)). The panel comprised representatives from 20 German medical societies, German patient representatives and experts from national and international institutions and authorities, including German regulatory agencies and academic centers (Supplementary Methods, Tables 1 and 2).

A steering committee (Supplementary Methods, Table 3) supervised the process, supported by neutral methodological guidance from AWMF representatives. Six topic-specific working groups were convened (Supplementary Methods, Table 4). After an initial online meeting defining key questions and literature search strategies, each working group conducted independent literature reviews and drafted recommendations with supporting background texts.

Recommendations were discussed and voted on during six online consensus conferences neutrally moderated by an AWMF representative. Voting included plenary discussion, amendments where necessary and formal voting. The strength of recommendations was determined by standardized wording and grading (Supplementary Methods, Table 5): strong recommendations were expressed using the wording 'we recommend/we do not recommend' or 'should/should not' (grade A); conditional recommendations were expressed using 'we suggest', 'ought to' or 'can/cannot' (grade B); and open recommendations were expressed using 'may be considered', 'could be considered' or 'might be considered' (graded as 'Optional'). The strength of consensus was classified according to predefined categories (Supplementary Methods, Table 6) based on the proportion of approving participants: strong consensus (>95%), consensus (>75–95%), majority approval (>50–75%) and no consensus (≤50%). Expository content describing specific facts, circumstances or problems without direct recommendations for action was designated as 'statements'; these did not require formal voting and were not assigned a formal level of evidence. The guideline is valid from 5 January 2026 to 29 June 2030. The revision will be initiated by the steering committee that will also review the need for updates to the guideline annually. Full methodological details are provided in the Supplementary Methods.

All participants submitted conflict of interest (COI) declarations via the AWMF online portal (Supplementary File 1). Moderate COIs were identified for seven individuals, who were excluded from leadership roles. To assess any potential influence, the consensus analysis was repeated both including and excluding their votes. As the results were unchanged, their voting did not affect the final consensus outcomes. The guideline was externally reviewed, adopted by

participating societies and circulated for review and support by international societies, organizations and stakeholders (Supplementary Methods, Tables 7 and 8).

A list of important abbreviations commonly used throughout this paper is provided in the Supplementary Explanations.

This guideline is directed at physicians involved in the treatment of bacterial infections in adult and pediatric patients, particularly those working in infectious disease management, antimicrobial stewardship and related medical and pharmaceutical fields. It further serves a broader audience, including clinicians outside the core specialties, pharmacists, patients and patient advocacy organizations, ethics committees, researchers in microbiology, infectious diseases and personalized medicine, regulatory bodies and public health authorities, policymakers, hospital administrators, health insurance providers and industry stakeholders in phage research and development.

General considerations and regulatory frameworks for phage therapy

Originally pioneered by Twort and d'Hérelle to combat enteric and wound infections, phage therapy fell out of favor during the antibiotic era. Today, however, the global crisis of antimicrobial resistance has sparked a renewed interest in these viral treatments^{1–6}. Phages are abundant in nature and the human microbiome^{7–13}, vary widely in structure and genome size and follow different life cycles, with lytic phages forming the basis of phage therapeutics^{14,15}. Moreover, the potential for bacterial resistance to phages requires continued monitoring and iterative adjustment during treatment. Available evidence suggests that phage therapy is generally safe when produced and administered according to quality standards, and first considerations for the use of phage therapy in clinical practice have been suggested to inform clinicians^{16–20}. In one series of 100 consecutive cases treated in Belgium, 77% of patients showed clinical improvement and 61% achieved bacterial eradication, with no serious phage-related adverse reactions²¹. Alongside the Belgian 100-patient case series, several systematic reviews have further characterized this field. A recent systematic review of safety and efficacy trials found that, although phage therapy is consistently reported to be safe in modern trials, efficacy has not been reliably demonstrated²². The authors attribute this discrepancy to key limitations in trial design, particularly the failure to deliver sufficient quantities of appropriately matched phages to the site of infection. Similarly, a systematic review focusing specifically on difficult-to-treat infections concluded that phage therapy shows a favorable safety profile and potential clinical benefit, particularly in compassionate-use settings, while emphasizing the heterogeneity of treatment approaches and the limited availability of controlled clinical data²⁰. Collectively, these findings support the overall safety of phage therapy and its therapeutic promise while underscoring the need for optimized treatment strategies and well-designed prospective trials to better establish efficacy.

Assessing phage activity relies on plaque, spot and liquid infection assays to generate phagograms, although reproducibility across laboratories remains limited.

The standard authorization pathway for medicinal products, based on randomized controlled clinical trials using investigational medicinal products manufactured according to Good Manufacturing Practice (GMP), presents major challenges for personalized phage therapy²³ (Fig. 1). Phage specificity requires individualized matching, which, alongside dynamic bacteria–phage interactions and the need for treatment adaptation, limits the standardization and scalability of such trials. Although early-phase studies suggest a favorable safety profile, the highly individualized nature of these treatments remains fundamentally incompatible with current regulatory frameworks^{24–30}.

Even outside the highly regulated environment of clinical trials, individualized phage administrations are often constrained by regulatory and practical barriers. GMP-grade phage manufacture is costly, time-consuming and often incompatible with the urgency and

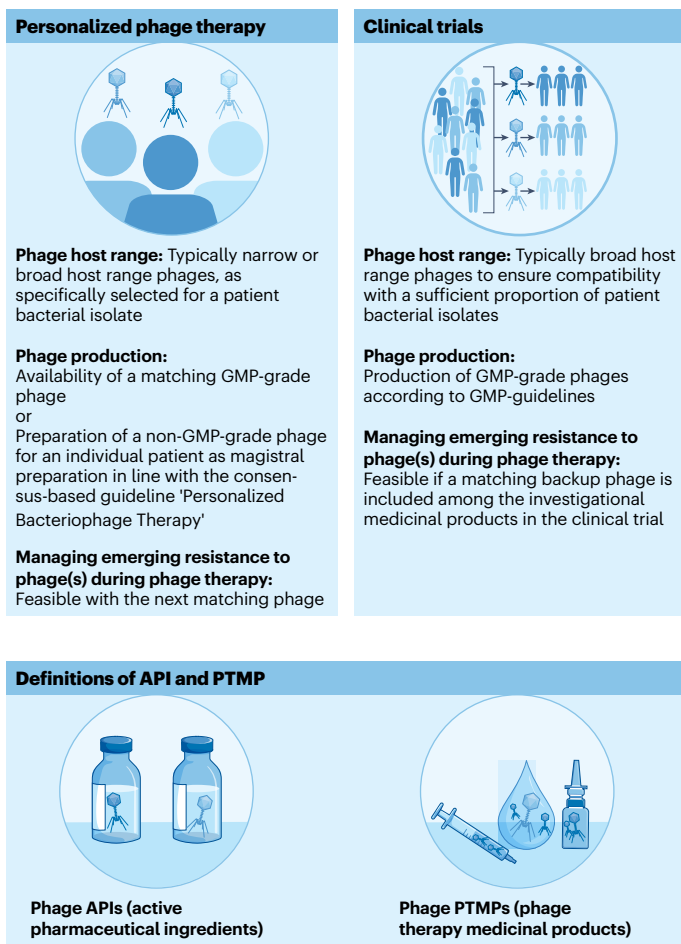


Fig. 1 | Overview of two main strategies using phage therapy. This schematic compares two main strategies in phage therapy: personalized phage therapy, which involves selecting or isolating phages tailored to the bacterial pathogen causing an infection in an individual patient, and phage therapy in clinical trials. The latter typically involves broad host range phages that can benefit multiple patients, often utilizing a selection of several phages, sometimes even combined as a phage cocktail. 'Emerging phage resistance' occurs when bacterial populations evolve mechanisms to avoid being infected by phages during phage therapy, similar to the way bacteria develop resistance to antibiotics.

flexibility required for and during personalized therapy, making it feasible for only a small subset of patients when suitable GMP-grade phages are already available. Consequently, many personalized treatments have relied on non-GMP-grade phages, as documented in case reports worldwide^{20,21,31–39}.

Magistral preparation of phage active pharmaceutical ingredients (APIs) – the purified phage preparations used as starting materials – and phage therapy medicinal products (PTMPs), which are the finished formulations intended for patient administration, offers a pragmatic alternative, as such preparations are generally exempt from GMP requirements. For example, in the European Union, under Article 3(1) of Directive 2001/83/EC, personalized phage preparations compounded as magistral formulations on prescription fall under this exemption. Nevertheless, existing professional guidance provides insufficient detail to ensure the consistent preparation of phage APIs or PTMPs. Although the European Pharmacopoeia (Ph.Eur) has recently issued baseline guidance for phage therapy¹⁶, the lack of detailed, practice-oriented standards continues to limit broader implementation. In most countries worldwide, the cross-border transfer of magistral phage preparations to individual patients remains challenging. Inconsistencies in quality standards, restricted and inflexible

manufacturing capacity, limitations in traceability and stability, including cold-chain requirements, liability and insurance issues related to transfers and logistical constraints at customs can all restrict flexibility and lead to substantial delays.

Given the growing number of patient requests and the limitations of existing regulatory pathways, this guideline emphasizes immediately applicable, patient-individualized approaches that complement industrial phage development rather than awaiting future legislative changes that may not address urgent clinical needs.

Recommendations on general principles of personalized bacteriophage therapy

Phage therapy should be considered on a case-by-case basis, mainly for patients in whom standard-of-care treatments have failed or are contraindicated. Outside clinical trials, phage therapy is typically applied within the framework of individualized treatment attempts, particularly for difficult-to-treat infections, which can be caused, for example, by antibiotic-resistant or biofilm-forming bacteria^{21,40–44}. Because phage therapy is highly specific (see also Supplementary Explanations, Fig. 1), successful treatment requires culture-based bacterial identification with species determination, followed by careful phage–bacteria matching. The susceptibility of the bacteria to the chosen phage(s) should be confirmed as close to treatment initiation as possible, as susceptibility to phages may change over time. In urgent situations, therapy may begin before susceptibility results are available and be adapted thereafter. In case of polymicrobial infections, all causative bacterial species should undergo phage susceptibility testing, as untreated bacteria may sustain an infection despite targeted therapy of a single organism, and comprehensive testing improves the likelihood of clinical success. Interdisciplinary discussions among treating physicians, microbiologists, infectious disease specialists and experts involved in phage selection, manufacturing, susceptibility testing and treatment are essential.

When quality standards are met, phage therapy appears safe^{16–18,20}. Despite limited evidence from clinical trials, the available data indicate no major safety concerns, including immunocompromised patients, children and pregnant or breastfeeding women^{18,20,21,28,45–74}. Beyond biologically expected responses (for example, fever and increased byproducts due to bacterial breakdown), no clinically relevant drug interactions or allergic reactions attributable to phage therapy have been reported, although monitoring remains advisable^{18,19,57,75,76}.

The guideline team proposes the following recommendations and statements on general principles of personalized phage therapy (Table 1). The full set of background explanations is provided in Supplementary Explanations 1.

Recommendations on infrastructure of personalized bacteriophage therapy

Safe, efficient and scalable implementation of personalized phage therapy requires a coordinated infrastructure that integrates laboratory diagnostics, phage preparation and clinical expertise. Core elements include access to phage laboratories capable of performing phage screening and susceptibility testing, appropriate facilities for phage preparation with defined quality control and safety standards and an interdisciplinary phage therapy board that brings together relevant medical specialists, infectious diseases experts, microbiologists and pharmacists to guide clinical case assessment and individual treatment strategies (Supplementary Explanations, Fig. 2). These components form an ideal, flexible framework and do not need to be housed at a single site; certain elements, such as phage preparation, may be outsourced to specialized centers.

Phage therapy is not limited to highly specialized centers, but any institution administering phages must meet minimum requirements, including appropriate storage conditions, medically qualified personnel and the ability to manage phage administration, safety monitoring,

Table 1 | Recommendations on general principles of personalized bacteriophage therapy

Recommendation/Statement	Grade of recommendation, strength of consensus
R2-1 Phage therapy may be considered for patients suffering from bacterial infections that might be treatable with phages, who qualify for an individual treatment attempt. This implies that standard guideline-based therapy has failed, is unavailable or is not applicable. Moreover, phage therapy may be considered within the context of a clinical trial.	Optional, consensus
R2-2 An interdisciplinary discussion between treating physicians, microbiologists and infectious diseases specialists, as well as experts involved in phage selection, manufacturing, susceptibility testing and treatment, should precede phage therapy.	A, strong consensus
R2-3 There is limited data on the safety of using phages in infants, children, pregnant women, breastfeeding women, patients with co-medications or allergies or immunocompromised patients. However, there is no data suggesting safety issues in these populations. Thus, treatment should be based on an individual risk–benefit assessment.	A, strong consensus
R2-4 The identification of the target bacteria for phage therapy should be culture based and include species identification and antimicrobial susceptibility testing.	A, strong consensus
R2-5 The susceptibility of the target bacterium to phage(s) should be confirmed as close to treatment initiation as possible.	A, strong consensus
R2-6 To identify the target bacteria for phage treatment, all relevant clinical information should be correlated with available microbiological results on a case-by-case basis. Ideally, this discussion should involve infectious diseases specialists and microbiologists. In the case of a polymicrobial infection, we recommend identifying the lead pathogen(s) responsible for the infection.	A, consensus
R2-7 The time interval between sample collection and start of therapy should be as short as possible. If renewed pathogen detection is not successful, phage therapy should be based on the last pathogen identification result.	A, strong consensus
R2-8 Phage therapy may be considered in life-threatening situations, even if phage susceptibility is unknown. This approach may be considered if broad-spectrum phage cocktails are available.	Optional, strong consensus
R2-9 In case of various different bacterial species responsible for infection pathogenesis, all of them should be sent for phage susceptibility testing.	A, strong consensus
S2-1 If it is not possible to identify the pathogen, personalized phage therapy is not feasible.	Not applicable ^a

^aNote that formal voting on statements was not required. Bolded sections highlight key recommendations. Information regarding the grade of recommendation and strength of consensus is available in Supplementary Methods, Tables 5 and 6.

concomitant therapies and microbiological sampling. Institutions without in-house capacities for phage assays, such as susceptibility or phage–antibiotic synergy testing, may rely on external laboratories, provided results are available in a timely manner. Standardized and harmonized methods for phage susceptibility and potency testing are essential, with an emphasis on interlaboratory proficiency testing. Referential guidance may be provided through recommendations currently under development by the subcommittee on phage susceptibility testing of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)⁷⁷.

Comprehensive documentation of phage therapy cases in national and/or international registries, including treatment protocols, outcomes and unexpected events, is considered essential to improve transparency, enable systematic evaluation and inform future practice⁷⁸. High-quality and harmonized data collection is viewed as critical for the long-term success of personalized phage therapy.

The recommendations and statements on infrastructure of personalized phage therapy are summarized in Table 2. A comprehensive list of all explanatory text is available in Supplementary Explanations 2.

Recommendations on preparation, quality control, labeling and storage of personalized phage therapeutics

Phage preparation for therapeutic use (Fig. 2) begins with the identification of suitable phages active against the bacterial target, which may be sourced from established phage collections or seed lots, environmental or human samples or synthetic and/or genetically engineered phages.

Genetically engineered phages may also be used to improve therapeutic suitability, for example by removing lysogeny-associated genes to ensure a lytic lifecycle. Notably, engineered phages have entered clinical evaluation, including CRISPR–Cas-enhanced bacteriophage cocktails targeting *Escherichia coli* in urinary tract infections (for example, LBP-EC01, phase 1b/2 clinical trials, [NCT05488340](https://clinicaltrials.gov/ct2/show/study/NCT05488340)) as well as in case reports covering other indications^{61,79}. However, such modifications may introduce risks, including recombination events, and entail additional regulatory and biosafety considerations, although this is not currently considered a major risk. It is advisable that their use be supported by thoughtful risk assessment and appropriate regulatory oversight.

Phage adaptation may be employed to enhance antimicrobial efficacy by evolving one or more phages on a patient’s clinical isolate to broaden host range or increase activity.

Phage APIs must be prepared from well-characterized phage and bacterial seed lot systems (Fig. 2 and Supplementary Explanations, Fig. 3) to ensure clonal origin, genetic stability and appropriate quality, including identity, potency, appearance, sterility and purity^{16,80–86}. For more information on the determination of these attributes, see Supplementary Explanations, Tables 1 and 2, and Supplementary Explanations, Figs. 3 and 4.

Phage preparation typically involves propagation of phages in defined bacterial hosts, followed by purification to remove bacterial impurities while preserving phage activity^{16,17,83}. Supplementary Explanations, Fig. 5 shows an overview of an upstream and downstream process, comprising bacterial cultivation and phage propagation followed by purification.

Table 2 | Recommendations on infrastructure of personalized bacteriophage therapy

Recommendation/Statement	Grade of recommendation, strength of consensus
S3-1 Personalized phage therapy requires an association with a dedicated infrastructure composed of the following interconnected modules: -Phage collections/banks -Clinical microbiology -Phage laboratory -Phage preparation facility -Pharmacy -Interdisciplinary clinical phage therapy board -Clinic	Strong consensus ^a
R3-1 The minimum requirement for physicians starting phage treatment should be board certification.	A, consensus
R3-2 When phage therapy is started, at least one board-certified physician should be physically available for supervision while the expertise required for additional input may be external.	A, strong consensus
R3-3 Physicians who perform phage treatments should be encouraged to participate in either national or international networks.	A, consensus
R3-4 Phage therapy should be documented, and data should be referred to a central registry, if available.	A, strong consensus
R3-5 Physicians performing treatment with phages should document their cases in a patient registry.	A, strong consensus
R3-6 Phage collections might make their phages accessible for scientific and potential therapeutic purposes.	Optional, strong consensus
R3-7 We recommend that all phage collections be considered as phage providers for phage treatment.	A, strong consensus
R3-8 Phage collections should provide clonal phages and, as a minimum requirement, information on the host strain of this phage.	A, strong consensus
R3-9 To facilitate/promote the connection of national/local phage collections, the introduction of a central management entity may be considered.	A, strong consensus
R3-10 We suggest the implementation of a harmonized template material transfer agreement (MTA) for phage providers providing phages for treatment purposes.	B, strong consensus
R3-11 Phage screening and phage susceptibility testing for target bacteria may be performed locally or centrally.	Optional, strong consensus
R3-12 Phage susceptibility testing methods should be harmonized between all laboratories performing phage susceptibility testing.	A, strong consensus
R3-13 We recommend that proficiency testing be performed.	A, strong consensus
R3-14 Local diagnostic laboratories should provide the target patient's bacterial isolate as well as identification and antibiotic susceptibility profiles.	A, strong consensus
R3-15 We recommend that local diagnostic laboratories providing phage susceptibility testing for phage therapy establish standard procedures. Those standard procedures should be guideline compliant.	A, strong consensus

^aNote that formal voting on statements was not required. Bolded sections highlight key recommendations. Information regarding the grade of recommendation and strength of consensus is available in Supplementary Methods, Tables 5 and 6.

Phage propagation requires a susceptible bacterial host. Ideally, these strains are selected from established master cell banks to ensure that they are free of resistance gene and mobile genetic elements or genetic elements supporting the synthesis of toxins or virulence factors¹⁶. Whole-genome sequencing can be used to verify the absence of these elements and any inducible prophage or phage-like sequences. In situations where no host strain matching the required phage from an established master cell bank is readily available, the patient's own clinical isolate may be used for PTMP preparation. In this case, undesirable genetic features do not necessarily disqualify the strain; because these elements originated within the patient, using the isolate as a production host introduces no incremental safety risk, provided a formal risk assessment is conducted (for more details, see also Supplementary Explanations, Table 2).

Cultivation conditions, including temperature, medium, duration, shaking and multiplicity of infection, must be optimized for each specific phage–host combination.

Phage APIs are formulated into PTMPs according to the intended indication and route of administration, potentially with excipients selected to enable effective delivery and enhance product stability. Formulations may be liquid, solid, semi-solid or device associated (for example, phage-coated wound dressing), supporting diverse administration routes. Stability and storage conditions should be validated to maintain safety and efficacy^{36,87–104}. PTMPs may be administered via multiple routes, including topical, intravenous, inhalational, oral, intravesical, intra-articular, intrathecal and others, and different routes may be combined as clinically indicated. Each API and PTMP must be accompanied by

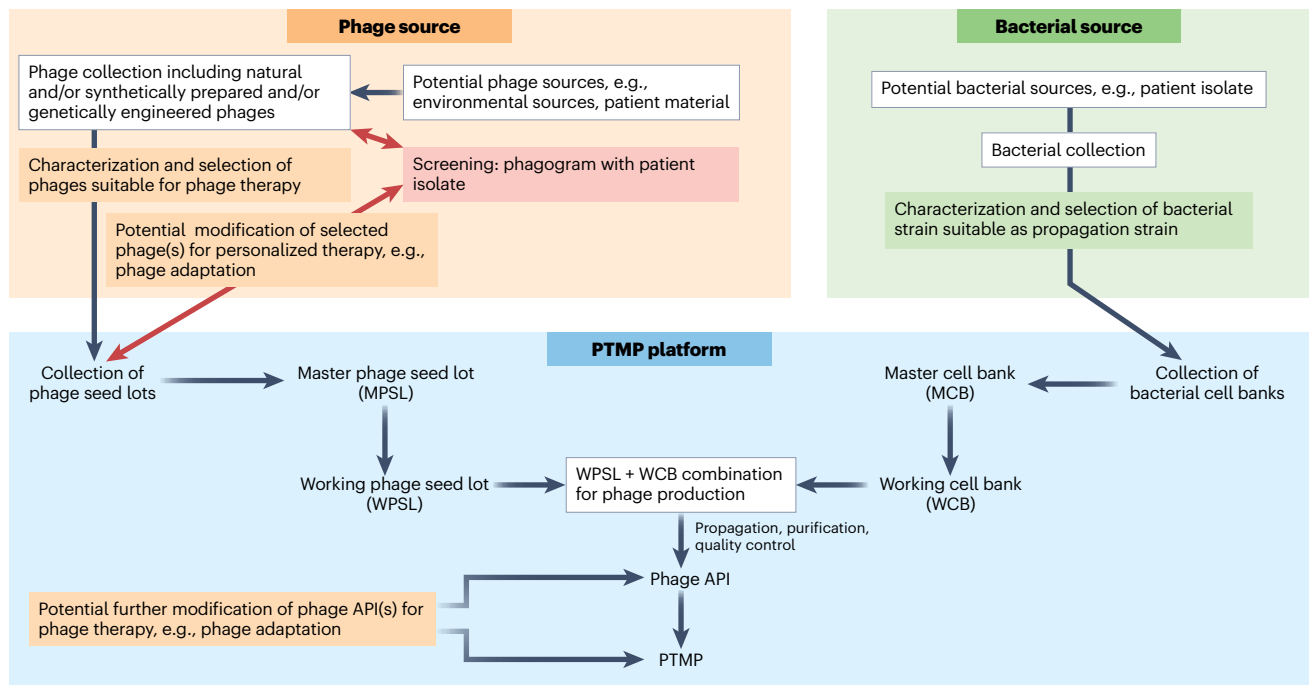


Fig. 2 | Overview of the pathway from bacterial isolates and crude phage lysates to phage therapy medicinal product. This figure was consented by guideline participants after an online survey (consensus).

a preparation label ensuring unambiguous identification as well as a supplementary information sheet providing detailed preparation-related information supplied separately from the packaging¹⁰⁵.

Although magistral preparations are exempt from industrial GMP, they must meet current scientific standards and be produced in controlled environments by qualified personnel⁸³. Quality control of phage APIs and PTMPs may be performed by qualified laboratories with appropriate phage expertise and in adherence to this guideline, using retained samples not intended for patient administration. Quality control steps include, as appropriate, identity, potency, purity and microbiological quality, pyrogenicity, genomic purity, protein contamination, prophages/temperate phages, pH, appearance, hemolytic activity and residual agents, with risk-adapted flexibility for urgent therapies. Supplementary Explanations, Table 2 details consented quality and safety requirements for (1) preparation environments such as air quality, (2) equipment, materials and preparation processes such as culture media, (3) phage seed lots such as identification, (4) phage APIs such as purification, (5) PTMPs such as stability in combined preparations and (6) bacterial working cell banks such as prophages.

Regarding the quality aspect of microbiological quality/sterility, non-sterile APIs or PTMPs must meet the microbiological thresholds defined in Ph.Eur. 5.1.4 and are intended for non-sterile administration routes such as oral, cutaneous or nasal use. Non-sterile APIs/PTMPs with high microbiological quality (Ph.Eur. 2.6.12 and 2.6.27) must achieve 0 colony-forming units (CFU) per milliliter or per gram and may be used for intravenous administration in emergencies, wound applications or short shelf-life products. Sterile APIs/PTMPs must comply with sterility requirements (Ph.Eur. 2.6.1 and 5.1.6) and are intended for intravenous use in non-emergency cases or for off-the-shelf preparations.

Endotoxin levels represent a critical quality attribute in the development of personalized phage therapeutics, as they directly influence purification strategies, formulation and the feasible dose for clinical application. Phage preparations require downstream purification (for example, anion exchange chromatography, endotoxin-binding resins, ultrafiltration and ultracentrifugation) to reduce endotoxins and host-derived impurities, with additional steps to remove process chemicals if needed. Endotoxin levels are quantified using standard

assays (for example, recombinant Factor C, monocyte activation test) and must be reported to ensure compliance of the final product with regulatory limits, typically approximately 5 endotoxin units per kilogram of body weight per hour (EU kg⁻¹ h⁻¹) for parenteral use^{106,107}, with possible route-dependent adjustments. For more details, see also Supplementary Explanations, Table 2.

Phage stability should be systematically evaluated using quantitative titrating methods, such as the double agar overlay (DAO) method, as described in the forthcoming Ph.Eur. General Chapter 2.7.38. Factors influencing stability include temperature, pH, ultraviolet exposure, ionic strength, purity, adsorption to matrices, shear stress and phage concentration^{91,108,109}. Testing under conditions reflecting intended use, including in biological fluids, can inform formulation, excipient selection and administration strategy. Storage conditions for each phage and formulation should be determined experimentally if not provided by the supplier (for more details, see Supplementary Explanations, Table 2, and Background R4-13–R4-15).

Consensus-based definitions related to the phage preparation process are provided in Supplementary Explanations, Table 1. The recommendations on preparation, quality control, labeling¹⁰⁵, documentation^{83,110} and storage of personalized phage therapeutics are summarized in Table 3, and the complete set of explanatory text is provided in Supplementary Explanations 3.

Recommendations on administration of personalized phage therapy

Phage therapy has been applied to a wide range of bacterial infections, particularly those affecting skin and soft tissues, bones and joints, cardiac devices, bloodstream and respiratory tract as well as the urogenital and gastrointestinal systems^{18,21,111}. Patient-centered planning of phage therapy should be individualized and take into account the patient's history of preceding antibiotic or phage treatments; prior interventions or surgeries; extent, localization and severity of infection; presence of prosthetic or other foreign material; underlying conditions; allergies; co-medication including ongoing anti-infective therapy; and overall clinical status.

Phage therapy should also be personalized regarding phage composition (single phage, sequential therapy or cocktails; see also

Table 3 | Recommendations on phage preparation and quality control

Recommendation/Statement	Grade of recommendation, strength of consensus								
R4-1 The search for suitable phages for the bacterial target can be performed using any suitable source, such as phage collections, collections of established phage seed lots, environmental sources, human sources including patient isolates and synthetic and genetically engineered phages.	B, strong consensus								
R4-2 Genetic modification of phage candidates, such as the removal of harmful determinants or lysogenic modules, can be used for phage therapy.	B, strong consensus								
R4-3 During propagation in the context of phage preparation, preference should be given to bacterial host strains that do not contain potentially harmful genetic elements.	A, strong consensus								
R4-4 Suitable bacterial propagation strains without prophages are rarely available but should be preferred for preparation whenever possible.	A, consensus								
R4-5 If no other more suitable bacterial propagation strain is available, the respective patient isolate should be considered as a propagation strain for the individual patient.	A, strong consensus								
R4-6 Phage seed lots used in PTMP preparation are clonal derivatives and should be characterized in detail (unless otherwise justified). This includes: •→Information on the phage source, isolation location and year •→Nucleotide sequence including the details of DNA/RNA extraction, sequencing, assembly and annotation, with the respective year •→Results regarding antimicrobial/biocide/metal resistances, virulence or lysogeny factors, with the respective year •→Known susceptible bacterial specie(s) and/or strain(s) •→Other parameters, such as plaque morphology or phage morphology, are determined, if relevant	A, strong consensus								
R4-7 Phage adaption should be an option to increase the efficacy of phage(s) to be considered for therapy.	A, strong consensus								
S4-1 The standard method to obtain therapeutic phages is the culture-based method.	Strong consensus ^a								
S4-2 Synthetic systems provide an alternative to culture-based methods to prepare phage APIs and PTMPs.	Strong consensus ^a								
R4-8 Quality control measures for APIs and PTMPs should include identity, potency, appearance, sterility/microbiological quality and purity (residual reagents, host cell impurities and contaminants). If applicable, pH (liquid PTMPs), water content (solid PTMPs) and pyrogenicity should also be controlled.	A, strong consensus								
R4-9 To meet the respective clinical needs, quality requirements of the APIs and PTMPs can be adapted depending on the indication, administration and formulation.	B, strong consensus								
S4-3 Qualified laboratories using validated methods are needed to perform quality control measures on APIs and PTMPs.	Not applicable ^a								
R4-10 Various formulations and administration routes exist for phage preparation, and the selection should be based on the specific indication and patient characteristics.	A, strong consensus								
R4-11 The preparation label should state ¹⁰⁵ :	A, strong consensus								
<table border="1"> <thead> <tr> <th>API</th><th>PTMP</th></tr> </thead> <tbody> <tr> <td>Name of the phage</td><td>Name of the phage(s); possibly other excipients</td></tr> <tr> <td>Titer (in PFU/mL) and total content (in mL)</td><td>Titer (in PFU/mL); possibly strength of other excipients; total content</td></tr> <tr> <td>Date of preparation Expiration date (or: recommended shelf life) Typical target bacteria</td><td>Date of preparation Route of administration Expiration date (or: recommended shelf life) Typical target bacteria</td></tr> </tbody> </table>		API	PTMP	Name of the phage	Name of the phage(s); possibly other excipients	Titer (in PFU/mL) and total content (in mL)	Titer (in PFU/mL); possibly strength of other excipients; total content	Date of preparation Expiration date (or: recommended shelf life) Typical target bacteria	Date of preparation Route of administration Expiration date (or: recommended shelf life) Typical target bacteria
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Table 3 (continued) | Recommendations on phage preparation and quality control

Recommendation/Statement	Grade of recommendation, strength of consensus
R4-12 The following information should be provided in the accompanying documentation (supplementary sheet)^{83,110}: →Qualitative and quantitative composition, including →Phage identity →Phage provider/manufacturer and contact details →Phage quantity (titer in plaque-forming units per milliliter (PFU/ml)) including date of (last) titrating →Identity of the host bacterium/bacteria used in the preparation process (to the strain level) →Typical target bacteria →If available: additional information on the host range →Pharmaceutical form →Recommended storage conditions. (Ideally, the phage supplier should provide validated storage conditions for each phage (formulation). If data is lacking, general storage conditions should be indicated (for example, storage in glass vials, temperature 4°C) with the notice that optimized storage conditions should be evaluated by the operating institution itself.) →Preparation date →Expiration date (including after opening) →Instructions for reporting serious adverse reactions and/or events →Instructions on how to dispose of unused (expired) phage preparations →For dried preparations: →The name, composition and volume of the reconstituting liquid to be added →The period of time within which the preparation is to be used after reconstitution →Presence of residues known to be harmful (for example, antibiotics, ethylene oxide) →Presence of phage and/or host characteristics known to be harmful (for example, damaging genetic determinants, lysogeny, transduction, prophages) →Bacterial residues such as (endo)toxins →Certificates of analysis of all components of the preparation →Instructions for opening the container/package →Publications referring to the phage	A, strong consensus
R4-13 The stability of the phage(s) in the respective preparation and administration mode should be ascertained.	A, strong consensus
R4-14 The appropriate storage conditions for APIs and PTMPs should be evaluated for each phage (formulation).	A, strong consensus
R4-15 If a phage product is supposed to be stored for a longer time, the shelf life (or, for unlicensed phage preparations, recommended storage time) should be determined for each phage and formulation according to individual stability tests, including phage activity, microbiological quality, pH and, where relevant, water content and excipients.	A, strong consensus
R4-16 Unlicensed APIs or PTMPs used in personalized phage therapy may have their recommended storage time extended if their potency and microbiological quality are guaranteed by thorough retesting.	Optional, strong consensus
R4-17 If unlicensed APIs/PTMPs are stored beyond their recommended storage time, their microbiological quality and efficacy should be verified by periodic determination of the following parameters: →Phage titer →Microbiological quality →pH →Where relevant, stability of supplementary preparations such as excipients	A, strong consensus
R4-18 Supplementary Explanations, Table 2 is R4-18.	A, strong consensus

*Note that formal voting on statements was not required. Bolded sections highlight key recommendations. Information regarding the grade of recommendation and strength of consensus is available in Supplementary Methods, Tables 5 and 6.

Supplementary Explanations, Fig. 6), dose, route, formulation, timing, frequency and duration, with adjustments made dynamically during therapy^{18,112–126}. Optimal phage titers depend on bacterial density, growth rate, site-specific conditions and administration route, acknowledging that excessive or insufficient titers may compromise efficacy. Phage stability during preparation and delivery, including potential losses from administration devices or gastric acidity, must be considered^{89,94,127–130}. Detailed explanations on how to address these aspects, including the use of phage cocktails versus sequential therapy and phage titer, are provided in Supplementary Explanations 4.

After comprehensive patient counseling and informed consent, treatment is generally initiated in an inpatient setting, with monitoring of vital signs, laboratory markers, microbiological cultures including ongoing phage susceptibility testing during phage therapy and, where appropriate, analyses of phage distribution at the target site and immune responses.

Follow-up duration after phage therapy should be established through interdisciplinary decision-making involving phage experts, microbiologists and infectious disease specialists. Informed by prior experience, follow-up should ideally be at least several months, extended for chronic infections where feasible, and harmonized with other infection management strategies.

A summary of the recommendations on the administration of personalized phage therapy is presented in Table 4, with the complete background available in Supplementary Explanations 4. A representative draft of an informed consent form is included (Supplementary File 3).

Recommendations on future research priorities to improve implementation and efficacy of phage therapy

Despite growing interest in phage therapy as a potential alternative or adjunct to antibiotics, the current clinical evidence base remains

Table 4 | Recommendations on application of personalized phage therapy

Recommendation/Statement	Grade of recommendation, strength of consensus
R5-1 The following aspects should be taken into account to properly plan phage therapy: →Patient history, such as prior antibiotic therapy, previous interventions and surgeries →Previous therapy with phages →Extent, localization and severity of the infection that should be targeted using phage therapy →Presence of prosthetic material, other implants or other foreign material in the body →Underlying conditions, allergies and co-medication, including ongoing antibiotic and other anti-infective therapy →Overall clinical status of the patient	A, strong consensus
S5-1 Obtaining informed consent is necessary.	Strong consensus ^a
R5-2 The choice of inpatient/outpatient setting should be based on an individual evaluation, including severity of the infection and general condition of the patient.	A, strong consensus
R5-3 Close monitoring of vital signs, as well as laboratory and microbiological parameters, should be performed before, during and after phage therapy, as clinically necessary for the specific case.	A, strong consensus
R5-4 Given the current state of scientific understanding, standardizing administration methods is not feasible, resulting in the absence of a singular method for any given indication. Therefore, decisions regarding administration should be tailored to each patient's individual treatment plan.	A, strong consensus
R5-5 In general, we suggest a phage titer (PFU/ml) of 1×10^6 to 1×10^9 be applied. If due to the administration route a phage loss is to be expected, we suggest the titer be adapted. Comment: During the endorsement process, this recommendation required additional clarification, with a strong reference to the background text.	B, strong consensus
R5-6 A follow-up of at least 1 year might be considered after phage therapy.	Optional, strong consensus
R5-7 If recurrence of an infection treated with phages is suspected, efforts should be made to confirm or rule out that the recurrence is caused by the same causative pathogen as the initial infection. Results should be documented and referred to a central phage registry if available.	A, strong consensus

^aNote that formal voting on statements was not required. Bolded sections highlight key recommendations. Information regarding the grade of recommendation and strength of consensus is available in Supplementary Methods, Tables 5 and 6.

limited. In particular, there is a notable lack of large, well-powered randomized controlled trials that comprehensively assess efficacy and optimize treatment regimens across indications. To date, only a small number of randomized controlled trials have been completed. For example, the PhagoBurn trial, which evaluated phage therapy for burn wound infections, highlighted both the feasibility and the challenges of conducting such studies, including issues related to phage stability, dosing and regulatory constraints²⁶. Similarly, a randomized trial in chronic otitis caused by *Pseudomonas aeruginosa* reported some evidence of clinical benefit, although the trial was limited by its small sample size and narrow scope¹³¹. Other controlled trials, including those investigating urinary tract infections and acute diarrheal disease, have yielded mixed or inconclusive findings^{24,28}. More recently, the Locus Biosciences trial targeting urinary tract infections provided additional evidence supporting the feasibility of phage-based approaches in this indication, although further validation is required¹³².

Notably, a growing number of clinical trials are currently ongoing or in preparation, reflecting increasing clinical interest in phage therapy. Collectively, existing and forthcoming trials underscore both the therapeutic potential of phage therapy and the substantial methodological and practical challenges that remain. Heterogeneity in study design, phage selection and manufacturing, dosing strategies and clinical endpoints further complicates direct comparisons across studies.

Given the impracticality of conducting trials for every phage–bacterium pairing, advancement of the field will require well-designed use cases, standardized outcome reporting (for example, through international registries such as Phagistry⁷⁸) and *n*-of-1 trial designs. Artificial intelligence and mathematical modeling are expected to accelerate phage research by enabling host–range prediction, reducing

laboratory screening and improving pharmacokinetic–pharmacodynamic optimization¹³³.

Key research priorities (Supplementary Explanations, Fig. 7) include systematic studies correlating clinical outcomes with laboratory-based phage susceptibility testing to improve prediction of therapeutic efficacy^{134–136}. In line, harmonization of susceptibility testing across liquid, solid and biofilm models, alongside the development of rapid diagnostic tools, is essential. Special attention is needed for biofilm-associated and polymicrobial infections, where predictive models remain weak.

Understanding phage–phage and phage–antibiotic interactions is another priority, as these combinations can be synergistic or antagonistic depending on context^{31,60,137,138}. Standardized methods to evaluate such interactions, including in polymicrobial settings, are required.

Phage-resistant bacterial variants frequently emerge during or after therapy, contributing to persistent infections and treatment failure²¹. Mechanistic insights into resistance development, including non-genomic adaptations, are critical for designing effective interventions. In addition, the evolutionary costs associated with resistance, such as reduced motility or restored antibiotic susceptibility, offer potential therapeutic leverage^{118,121,122,124,125}.

Phage behavior in patients can be affected by site-specific physiological conditions, including low pH, bile acids and ion concentrations^{139,140}. The host immune system might further modulate phage pharmacokinetics, with mechanisms such as phage endocytosis and pre-existing or induced antibodies^{141–143}, underscoring the need for systematic investigation to guide optimized administration strategies.

Effective clinical translation also depends on optimized phage formulation and delivery strategies to ensure stability, activity,

Table 5 | Recommendations on future research priorities of phage therapy

Recommendation/Statement	Grade of recommendation, strength of consensus
R6-1 Systematic preclinical studies to investigate the efficacy of phages in the laboratory setting (in vitro and in vivo) versus the treatment situation (in reality-near situations) should be conducted.	A, strong consensus
R6-2 Strategies should be developed that recommend specific approaches (such as testing in biofilm models or ex vivo, in vivo models) to increase the probability of high in situ efficacy.	A, strong consensus
R6-3 Fundamental research (preclinical trials) should be conducted on how phages impact infections caused by more than one pathogen (strain, species, genus) to model phage efficacy in clinical settings.	A, strong consensus
R6-4 In order to avoid antagonistic phage–phage and phage–antibiotic interactions and to find the optimal combination of antibiotics and phages, in-depth preclinical studies in research consortia should be conducted.	A, strong consensus
R6-5 Preclinical (in vitro and in vivo) studies investigating the occurrence of phage resistance should be conducted. These should include studies that (1) elucidate the probability of phage resistance for a particular approach, (2) investigate the relevance of phage resistance to therapy outcomes and identify mitigation strategies and (3) elucidate the exploitation of phage resistance that causes evolutionary costs.	A, strong consensus
R6-6 In the clinical setting, retrospective analyses of samples collected around phage therapy could be exploited to understand evolutionary pathways and to correlate data and findings made during in vitro and preclinical studies.	Optional, strong consensus
R6-7 Future research should consider the interaction with human physiology, including human cells and immunological aspects.	A, strong consensus
R6-8 The effect of adverse physiological factors, including, but not limited to, such as extreme pH values, extracellular proteases and bile acids, reflecting the infection site or relevant conditions, should be investigated to elucidate the pharmacology of phage therapy in the human body.	A, strong consensus
R6-9 To avoid situations during therapy that might negatively impact phage efficacy, preclinical studies (in vitro and in vivo) should be conducted to examine the interaction of the human body with phages, in particular with the adaptive and innate immune system.	A, strong consensus
R6-10 Safe and efficient methods for the delivery of therapeutic phages to the site of infection should be developed to ensure stability, including persistence and activity, or to reduce immunogenicity.	A, strong consensus
R6-11 The use of existing molecular biology tools and the development of novel techniques in order to create novel phages with a broader host range and optimized safety profile should be investigated.	A, strong consensus
R6-12 Preclinical studies (in vitro and in vivo) of bacterial receptor interaction with phage proteins could allow obtaining the knowledge required to create phages with less specificity and, thus, should be researched.	A, strong consensus
R6-13 To accelerate the preparation and downstream processing of therapeutic phage solutions, research should be conducted to develop rapid protocols and/or methods that allow the efficient purification of phages and the concomitant removal of undesirable substances such as endotoxins.	A, strong consensus

Bolded sections highlight key recommendations. Information regarding the grade of recommendation and strength of consensus is available in Supplementary Methods, Tables 5 and 6.

persistence and reduced immunogenicity. Innovations in encapsulation and nanoparticles, along with systematic evaluation of dosing, timing and treatment duration, are central for safe, effective and scalable phage therapies^{91–95,97,144}.

Targeted genetic modifications can expand the therapeutic scope of phages by altering receptor-binding proteins or removing lysogeny genes, thereby overcoming narrow host ranges or unlocking previously unusable temperate phages⁶³.

Current purification approaches, including endotoxin removal, are often labor-intensive and costly and reduce phage titers. Innovations such as cell-free phage production^{145–147} and optimized purification protocols are needed to enhance efficiency and maintain therapeutic potency.

In Table 5, we provide a summary of the recommendations; the full explanatory text is included in Supplementary Explanations 5.

Limitations

The major limitation of this consensus-based guideline lies in the scarcity of high-quality evidence informing its discussions and

recommendations. The current literature predominantly comprises preclinical and early-phase clinical trials, expert opinions and case reports or series. Consequently, for certain aspects, such as threshold definitions in phage quality control testing or PTMP dosing across different administration routes and clinical indications, precise values could not be specified, and recommendations were, instead, formulated based on the best available knowledge and expert consensus. In addition, as with any consensus-driven process, there is an inherent risk of suppressing minority perspectives and introducing bias related to participant selection and methodology. These challenges were addressed through a high degree of methodological transparency and precision, including the explicit indication of the strength of consensus for each recommendation. Furthermore, the guideline was developed by a multidisciplinary and international panel representing diverse areas of expertise and key stakeholder groups.

Conclusion

Healthcare professionals, pharmacists and patients are advocating for coherent, standardized frameworks to ensure the safe and effective

integration of personalized phage therapy into pharmaceutical preparation and clinical practice. This guideline represents, to our knowledge, the first detailed and consensus-based statement on personalized phage therapy. It offers practical, inspection-ready standards that expand upon existing, less detailed guidance, supporting implementation in pharmaceutical and clinical settings. Its interdisciplinary and international development concept ensures broad applicability across medical specialties and healthcare systems worldwide. The final consensus statement provides over 60 recommendations and statements covering general principles, infrastructure, phage preparation and quality control, clinical application and research topics, which together form a comprehensive framework for establishing phage therapy as a legally compliant, high-quality and safe treatment option when antibiotics fail. Although intended for international application, we acknowledge that adaptation to the legal and regulatory nuances of local jurisdictions might still be needed. Moving forward, this guideline might serve as a foundation for global harmonization, regulatory refinement and the integration of phage therapy into routine patient care.

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Medicine is subject to an ongoing development process, so all information, especially regarding diagnostic and therapeutic procedures, can only reflect the knowledge available at the time of the publication of the guideline.

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Author contributions

S.W., S.L.J., M.J.G.T.V. and A.Y.C. coordinated the structured guideline process in accordance with the framework of the AWMF in Germany and drafted the manuscript. All authors, except the external reviewers (T. Faltus, P.R. and H.B.), were actively involved in the subgroup work and the preparation and/or discussions of the six consensus conferences and contributed to the manuscript. All authors reviewed and approved the final version of the manuscript.

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Additional information

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