A roadmap for supporting the development of advanced therapy medicinal products in a European framework

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Summary

Advanced therapy medicinal products (ATMPs) represent a paradigm shift in medicine; however, their implementation in European health systems is often hampered by EU regulations. Amidst a rapidly evolving and increasingly competitive global landscape, dominated by the US and China, it becomes imperative that Europe strengthens its position. This requires establishing a dialogue with European authorities to devise new regulatory mechanisms and incentives paving the way for innovation in drug development and implementation. Here, experts from the European University Hospitals Alliance (EUHA) specialising in ATMPs, share their vision on changes needed at the regulatory and organisational level to incentivise the development and clinical use of ATMPs and ensure an equitable and fast access for patients, largely inspired by the problems encountered in an academic

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environment and in developing ATMPs for rare diseases. To achieve real-world impact, these solutions should be supported by competent authorities at regional, national, and EU levels.

Keywords: Advanced therapy medicinal products (ATMPs); Equitable clinical implementation of ATMPs; Regulatory framework for ATMPs; Clinical development of ATMPs; Manufacturing of ATMPs; Reimbursement of ATMPs; Decentralised production of ATMPs; Hospital exemption; Real world evidence

Introduction

Advanced Therapy Medicinal Products (ATMPs) have opened new treatment options for many diseases, including some previously untreatable ones. They differ from conventional drugs and tissues in their manufacturing, quality control, mechanisms of action, and frequent single-use administration. Most marketed ATMPs are in vivo or ex vivo gene therapies, while somatic cell and tissue-engineered products remain rare. Some tissue-engineered products that were available as transplants disappeared from the market after reclassification under the ATMP Regulation. Because development, regulation, and uptake vary by category, frameworks must adapt to their specific needs.

The new regulation for products derived from substances of human origin (SoHO)[1] (effective 2027) establishes a non-profit framework, potentially enabling faster and more equitable access, particularly for minimally manipulated somatic cell and tissue-based therapies. While SoHO does not alter ATMP definitions, debates continue over whether EMA's Committee for Advanced Therapies' (CAT) interpretation is too broad,[2] and clearer guidance from the European Commission (EC) or EMA is needed.

Given their complexity, high costs, and remaining uncertainties about side-effects and long-term outcomes, ATMPs should for now be limited to carefully selected patients in specialised centres with the infrastructure to ensure safety, follow-up, and equitable access. Their distinctive features and pricing challenge current legal, regulatory, and financial frameworks, underscoring the need for adaptation to enable wider clinical implementation.

To ensure equitable access of patients to ATMPs, it is essential to create a dense network of European ATMP-hubs, and to facilitate market access for academic organisations such as universities and university hospitals as well as small and medium-sized enterprises (SMEs). Academic institutions and SMEs—many of which originate from publicly funded research in academic institutions-are the main drivers of pre-clinical ATMPs development. University hospitals also play a central role in first-in-human clinical studies, leveraging their expertise and disease knowledge.[3] However, despite highly promising preclinical results, many of these academic ATMP candidate products fail to progress to clinical trials, largely due to limited resources and lack of knowledge on how to navigate the complex regulatory pathways.[4] While academic centres may sometimes be able to conduct early-phase (I/II) clinical trials, late-stage development remains dependent on large biotech and the pharmaceutical industry, particularly in the field of oncology.[5] Consequently, many promising ATMPs do not reach the market, partly because pharmaceutical companies often prioritise high-incidence indications over rare diseases–the target of many ATMPs.[6] Moreover, limitations in central production capacity lead to companies prioritising larger countries willing to pay higher prizes.

Hospital-based ATMP production platforms could help to overcome these capacity limitations. In particular, autologous ATMP treatments—tailored to individual treatments-require intensive, personalised interaction with healthcare professionals, making them less suited to pharmaceutical-scale manufacturing. This reinforces the case for decentralised, academic-led, point-of-care production, especially for rare diseases.

Finally, the exceptionally high prices of commercially developed ATMPs constitute a major roadblock to widespread clinical use. Companies justify these costs by citing elevated research investment, the life-saving potential of these therapies, the complexity of production abiding with current regulatory requirements, and the offsetting of long-term healthcare costs associated with rare diseases.[7] However, regardless of the validity of these claims, it is evident that large-scale adoption of ATMPs at current pricing levels would be unsustainable for solidarity-based healthcare systems, both in terms of total cost and cash-flow.

ATMPs also exemplify a broader concern within the academic community; namely that Europe's current complex regulatory environment is increasingly hampering innovation. Regulatory hurdles are often cited as a reason for innovators relocating development of their products outside of the EU. Regulatory simplification, greater flexibility, and Europe-wide harmonisation are essential if Europe is to remain competitive in the global innovation race.

Pre-clinical development and manufacture of ATMPs

Enhancing the regulatory incorporation of alternative methods for pre-clinical testing of ATMPs

The pre-clinical assessment of ATMPs presents challenges not fully addressed by conventional frameworks. Standard methods for proof-of-concept, toxicology, and bio-distribution often fail to translate as animal models are poor predictors of clinical outcomes.[8,9,10,11,12] Current regulations, relying on assumptions for conventional drugs such as predictive animal models and standardised manufacturing, can be impractical or uninformative. This highlights the need for more flexible approaches that ensure safety while enabling translation to the clinic. Emerging in vitro alternatives to animal testing, such as organoids, 3D-clusters of cells derived from stem cells that mimic specific tissues and advanced modelling using artificial intelligence need to be studied and incorporated into the pre-clinical route. Additionally, new gene editing technologies raise new safety concerns, reinforcing the need for adapted pre-clinical evaluation strategies. A minimum set of standardised parameters and corresponding models customised to specific ATMP types should be defined by EMA to guide the progression toward first-in-human clinical testing. For in vivo gene therapies, bio-distribution and vector tropism modelling are essential, for ex vivo gene-modified cells, off-target effects and long-term engraftment are safety assessment challenges. Tissue-engineered products often require biomechanical and functional assays that are not adequately represented in current preclinical models. Early and sustained dialogue between developers and regulatory bodies will be critical to align expectations on efficacy and safety benchmarks.

Particular attention must be paid to the specificity and safety of the genetic modifications. Minimising off-target effects, malignant transformation risks, and immunogenicity requires the development of new testing protocols. Technologies recently introduced such as CRISPR/Cas9 present unique challenges that need to be addressed. Moreover, as 'living drugs', many ATMPs may differentiate and continue to evolve after administration, adding further complexity to preclinical evaluation.[13]

Investment is needed to develop and validate innovative, non-animal preclinical models. Regulatory frameworks must remain flexible to integrate these methods, ensuring robust evaluation while enabling timely ATMP translation. The EMA, with the EC and national authorities, should define harmonised ATMP-specific requirements and validate alternative in vitro and in silico models for regulatory use.

Standardising and decentralising ATMP manufacturing in Europe

Standardised and decentralised manufacturing, particularly in academic centres, could improve equitable ATMP access. This does not imply that every infusion centre must produce on site; for larger indications (e.g. multiple myeloma, diffuse large B-cell lymphoma), a hub-and-spoke model, with a limited number of manufacturing hubs supplying multiple infusion centres, may be more efficient. Given the diversity of ATMPs, multiple disease-specific networks will be needed, developed stepwise through pilot projects, gradual upscaling, and regular review. Autologous cell therapies may benefit most from point-of-care production to optimise logistics, while in vivo gene therapies and some tissue-engineered products are better suited to centralised manufacturing with economies of scale. Decentralisation could shorten vein-to-vein times,[14] though evidence is limited. EU-funded pilots, coordinated by EMA and national GMP inspectorates, should test feasibility and quality outcomes. Such models also offer the potential for future-proof high-throughput and cost-effective manufacturing, potentially based on validated closed systems that may reduce the requirement for class B classified environments.[15] Early steps in this direction have already been taken, with a regulatory framework for point-of-care ATMP manufacturing recently introduced in the UK.[16]

The newly revised EU risk-based Good Manufacturing Practice (GMP) guideline for ATMPs,[17] has introduced greater flexibility for standardised manufacture. However, some challenges remain. There is a need for an effective regulatory framework adapted to the unique requirements of small-scale and decentralised production methods. This should be accompanied by comprehensive guidelines for pharmaceutical-grade raw materials, including those from biologic or human origins, to enhance quality, precision, purity, functionality, reproducibility, and stability of the end products. Moreover, tailored quality control standards for technical equipment and structured training of personnel specialised in GMP-compliant ATMP manufacture are essential for ensuring regulatory compliance and product integrity.

Equally needed are uniform guidelines for GMP simulation and GMP-like production facilities, where respectively new production processes can be made operational prior to their implementation and where ATMPs can be produced according to less stringent criteria. Reliable and clinically relevant potency assays for ATMPs, along with quality assays for materials like cells and vectors obtained from non-industrial suppliers are also urgently needed. Given the inherent biological variability of ATMPs, strict quality control measures throughout the production process are critical to minimise batch-to-batch inconsistencies. Notably, the establishment of standardised platforms with validated procedures for the preparation and testing of related products, has the potential to streamline and accelerate the manufacturing of complex ATMPs.

Currently, most development of manufacturing methods occurs at academic institutions or SMEs. However, transferring these manufacturing methods to larger entities capable of cost-effective, high quality and safe marketing is often problematic. The development of common best practices and "automated" production platforms could greatly support this transition and increase manufacturing scalability.

Although the EU has defined a regulatory framework for GMP-compliant ATMP manufacturing, variability in its interpretation across individual Member States (MS) persists. Since MS oversee national GMP governance, inconsistencies in ATMP production and quality controls may arise, potentially limiting cross-border standardisation. Addressing these differences is crucial to enable harmonised, decentralised manufacturing of ATMPs across Europe.

Establishing a limited number of decentralised regional academic manufacturing platforms, supported by clear regulatory and logistical frameworks, and standardisation for testing, validation, usage of raw materials, quality control, as well as outcome measurement and long-term follow-up of patients, could streamline the development, approval, and distribution of ATMPs. Such an approach would help ensure consistent product quality, enhance patient access, and foster innovation within a unified European market.

Clinical development of ATMPs

Enhancing clinical development pathways for academic and non-profit ATMPs

Among the major bottlenecks for the development of academic ATMPs are the regulatory hurdles and the limited availability of funding for supporting their clinical development. The costs associated with advancing an ATMP to marketing authorisation (MA) are very high, largely due to the complexity of manufacturing, the expense of clinical trials, and the stringent regulatory standards on safety and quality.

Several initiatives have been launched to address these barriers while maintaining high standards of patient safety.[18] Notably, the European Medicines Agency (EMA) has identified 'Support translation of advanced therapy medicinal products into patient treatments' as a strategic priority.[19] However, current recommendations remain too general and their effectiveness in facilitating patient accessibility and supporting continued innovation and clinical translation will need to be critically evaluated. The proposed revision of the European pharmaceutical legislation also envisages a simplification of procedures that is expected to benefit SMEs and non-commercial entities involved in the early development of medicinal products. While the legislation itself will set the overarching framework, the detailed provisions for adapted clinical trials, use of Real-World Evidence (RWE), for sample size definition and comparative analysis, secondary use of health data, and regulatory sandboxes would need to be defined in ad hoc regulatory guidelines developed by EMA and other competent authorities.

Building on these initiatives, the EUHA advocates for a dedicated non-profit pathway to MA, to increase patient access to ATMPs. Such a pathway should include reduced or waived regulatory fees, enhanced procedural support, and build on the EMA's pilot program providing tailored guidance to academic and non-profit sponsors addressing unmet needs. The EMA and EC should further develop this approach and ensure that Horizon Europe and EU4Health include targeted calls for Technology Readiness Levels (TRL) 4–8 activities, bridging the funding gap between preclinical work and late-stage trials.

In parallel, sustainable public funding mechanisms should ensure that public funding for clinical trials and regulatory procedures is available for breakthrough ATMPs from academia or non-profit organisations. Currently, public funding schemes tend to prioritise basic research and early-stage innovation, often excluding activities related to clinical trials or safety studies, which correspond to TRL 4 and above in the EU. Consequently, scaling up an ATMP becomes unfeasible due to insufficient funding. Addressing this gap would require public research agencies, health technology assessment bodies, and insurance funds to invest more in the clinical and regulatory development phases of breakthrough ATMPs. This will require the political will to invest more public money into ATMP development but also pooled cross-border co-funding mechanisms of HTA bodies, and insurers or through non-profit vehicles or established EU programs. Strenghtening collaboration between academic researchers, industry partners, and regulatory agencies is also critical to overcome the barriers for development and translation of ATMPs. Increased support for partnerships and collaborations, including funding, infrastructure, and regulatory support can accelerate the development of promising ATMPs, ensuring they are brought efficiently from bench to bedside across Europe.

Ensuring access for commercially non-viable ATMPs through harmonised use of hospital exemption (HE)

HE provides an important access route for ATMPs that are not commercially viable, particularly rare-disease somatic cell therapies and certain tissue-engineered products—rather than high-profile gene therapies with clear industrial interest. Its implementation, however, varies widely across MS. Some restrict HE to individual cases (e.g. Belgium, the Netherlands, Italy), while others (e.g. France, Germany, Spain) apply it more broadly, allowing temporary conditional use under strict standards of quality, traceability, pharmacovigilance, and clinical evidence. Data collected under HE may support a future MA while costs are reimbursed by health authorities.

EUHA supports a harmonised and accessible HE framework across Europe, ensuring that products meet equivalent safety, quality, and efficacy standards to preserve the credibility of academic ATMPs. This does not imply mutual recognition of HE approvals across MS, which would undermine the EMA's role, but rather harmonisation of eligibility criteria, quality standards, and data requirements. Patients from other MS could then access treatment at producing centres under their HE without bypassing EMA evaluation. The EC's recent report confirms that National Competent authorities will report safety and efficacy data on HE-ATMPs to the EMA, which will create a central repository.

Harmonisation should include shared registries, cross-border access mechanisms, and integration of HE data into regulatory submissions if MA later becomes feasible. Flexibility must be matched with safeguards to prevent misuse by commercial actors, with EMA guidance supporting consistent interpretation and the EC ensuring alignment with broader regulatory simplification efforts.

HE should be seen as complementary to other pathways. While the non-profit MA pathway and Conditional Marketing Authorisation (CMA) provide EU-wide authorisation for products with market potential, HE addresses unmet needs for small populations when a full MA is not feasible and can act as an interim access mechanism while data are generated. Clear guidance from EMA and the EC on how these pathways operate sequentially or in parallel would strengthen oversight, avoid duplication, and accelerate safe translation of innovation into practice.

Facilitating ATMP market entry through adaptive clinical trials and real-world evidence (RWE)

Standard drug evaluation requiring large randomised trials is often impractical for ATMPs, particularly in rare diseases, precision medicine, and frail populations. In these cases, traditional phase I/II/III designs can hinder development, and randomisation against placebo or standard of care may be unethical where no effective treatment exists and the possibility of crossover is not sufficient to prevent patients randomised to a placebo arm from experiencing significant disease progression during the trial. For example, the ASPIRE-FTD Phase I/II trial of AVB-101 in progranulin-related frontotemporal dementia uses a single-arm design. Such designs are often unavoidable in ultra-rare gene therapy indications, while larger comparative trials may still be feasible for some oncology cell therapies. Tissue-engineered products may require long-term functional endpoints distinct from pharmacological trials.

Alternative methodologies—such as single-arm trials with indirect or external comparators and adaptive designs—are already accepted by regulators and used in industrial ATMP development. Single-arm studies can be strengthened with natural history cohorts, registries, or other real-world data (RWD). Adaptive designs, when pre-specified in protocols and statistical plans, allow modifications such as sample-size re-estimation or early stopping without compromising trial integrity. These approaches must use rigorous biostatistics to avoid selection bias, multiple testing issues, or post-hoc adaptations that could create misleading results.

RWD use in ATMPs remains challenging. GDPR constraints, ethics approvals, and fragmented, product-based registries complicate comparative analyses, particularly in rare diseases. Registry duplication—post-marketing, national, and disease-specific—adds to the burden for clinicians. The EMA has often required ongoing RWE collection as a condition of approval (e.g. Zynteglo for β-thalassaemia in 2019). An integrated EU-wide pharmacovigilance and RWD system would reduce costs and uncertainties while ensuring robust post-marketing evidence.

A coherent EU strategy is urgently needed. This should include high-quality, disease-specific registries coordinated with scientific societies, interoperable data models to address privacy, and harmonised frameworks for RWD use in regulatory and reimbursement decisions. An adapted approval pathway for ATMPs should explicitly support RWD and adaptive designs, with clear conditions for their integration into marketing applications. The EC, EMA, HTA bodies, and scientific societies should jointly coordinate a federated EU-wide RWE infrastructure to avoid duplication and ensure post-marketing data meet regulatory and payer requirements.

Adaptive governance models for clinical trials and RWE

Unlike traditional drugs, first-in-human trials with ATMPs usually are combined phase I/IIa trials and enrol critically ill patients. It is also generally accepted that particularly for ATMPs, potential toxicities are rarely detectable in preclinical studies,[12] and cannot be adequately addressed for ATMPs.[20] Therefore, appropriate risk reduction measures are important in ATMP clinical trials. These include close monitoring and rapidly accessible treatment options (e.g. in intensive care units) by fully trained medical professionals in specialised centres.

To respond to the evolving knowledge base, a so called "adaptive governance" model has been proposed.[21] This model includes addressing public safety concerns in relation to accelerated authorisation mechanisms, longer follow-up periods and implementation of extensive post-marketing safety and efficacy studies. The post MA assessment of safety and efficacy is commonly referred to as RWE by analysing RWD. In the "Regulatory Science to 2025 strategy",[19] EMA has promoted the use of RWD and big data in decision-making processes.

In this context, EUHA emphasises the importance of ensuring that early-phase ATMP trials are conducted in

centres with demonstrated capability of ensuring patient safety, coordinating long-term follow-up, and contributing to a high-quality, continuous evidence base. We recognise that, at the time of submission of the clinical trial application (CTA) and the investigational medicinal product dossier (IMPD), the relevant national competent authority already conducts an in-depth assessment of the proposed centre(s)' capabilities. Our recommendation is not to pre-empt this evaluation, but to highlight the value of a coordinated network of expert centres with established expertise and infrastructure for ATMP trials, that would support both better outcomes for patients and more robust long-term data generation.

A financial framework for ATMPs

Innovative reimbursement models for sustainable patient access

A fundamental challenge for academic and industrial ATMP developers and healthcare systems (and payers) is to find a model that finances clinical use of ATMPs in a long-term and economically sustainable manner. Although a high price may be justified by a large health benefit, the short-term budgetary impact may be so high as to prevent paying for the new treatment. How to demonstrate the value of an ATMP treatment already at an early stage in the development? How can a payment model be designed for a treatment that only needs to be given for a short period of time and that potentially could generate a value that accumulates over an extended time post-treatment? ATMPs often reach the market before long-term safety and efficacy data will become available. Prolonging the period prior to MA to assess long term data would also delay access for patients to life-changing drugs. Therefore, new payment models are needed and ATMP developers must already consider cost-effectiveness and short-term budgetary constraints when designing the development process.

Although MA for ATMPs in the EU is centralised, it is still the individual MS that assesses health economics of ATMPs and sets prices. In this assessment, different national or local priorities as well as the use of different assessment methods may lead to different outcomes. There is yet no agreement on a common health economic model to measure the effects of ATMPs. In addition, the payment systems for ATMPs also differ between MS. Furthermore, industry is not obliged to ensure equal access to their products all over Europe and MA does not mean equal access to ATMPs all over Europe. Central production bottlenecks on the industry side as well as highly variable health economic conditions of the European healthcare systems affect implementation in standard-of-care negatively.

EUHA proposes innovative and EU-harmonised pricing, reimbursement and procurement solutions to be adopted by the EU and national frameworks once an ATMP becomes standard-of-care.

For SoHO-derived ATMPs, the Council of Europe recommends regulating the profits to avoid commodification and ensure that pricing reflects production costs and reasonable margins rather than market scarcity. Incorporating such principles into EU and national reimbursement frameworks could enhance equity, particularly for cell therapies and tissue-engineered products where donor-derived materials are a critical component.

Pricing, reimbursement and procurement solutions may include: (i) sharing data for reimbursement and uniform adoption of an innovative reimbursement model across EU MS (i.e., one type of product = one type of reimbursement model); (ii) adoption of value-based pricing models using Managed Entry Agreements to mitigate the risks due to uncertainty in data provided at the moment of price negotiation or dynamic pricing that can change over time according to the evidence collected; (iii) centralised European negotiation of pricing and joint procurement to improve equal access, (i.e. one type of product = one type of contract for all EU countries) similar to pricing and procurement used for COVID-19 vaccines; and (iv) overcoming market fragmentation to facilitate cross-border access to treatments, with particular regard to ATMPs that will not become available in all countries (e.g. for ultra-rare diseases). For in vivo gene therapies with a one-time administration and durable effect, annuity or outcome-based payment models may be appropriate. In contrast, some tissue-engineered or cell therapies may require repeat administration or ongoing monitoring, calling for different reimbursement structures.

By addressing the financial and organisational challenges in parallel with regulatory and clinical reforms, the EU can ensure that innovative ATMPs are not only authorised but truly accessible to all patients who may benefit.

A centralised European (and beyond-EU) price negotiation is highly unlikely in the short term given Member State sovereignty concerns. In the meantime, the EC should encourage voluntary joint procurement agreements, as in Beneluxa or Valletta, and pilot cross-border reimbursement schemes for ultra-rare ATMPs.

Conclusion

ATMPs represent a paradigm shift in the treatment of serious and rare diseases, offering transformative opportunities where traditional therapies have fallen short. However, their distinct nature–from manufacturing and quality control to their mechanism of action and single-use administration-demands a regulatory framework adapted to their specific challenges. At this early stage of clinical implementation, uncertainties about long-term efficacy and safety remain, necessitating both vigilance and innovation in regulation.

The current EU regulatory environment, while designed to protect patient safety, risks hampering clinical development and limiting patient access to these groundbreaking therapies. Without targeted reforms, Europe may fall into a competitive disadvantage in ATMP innovation and compromise equitable access, particularly for patients suffering from ultra-rare and commercially non-viable conditions. It is therefore essential to facilitate market access for non-profit organisations such as universities and university hospitals. We recognise that our proposals to incentivise and accelerate safe and equitable ATMP access, come with important practical hurdles. Identifying "breakthrough" ATMPs and funding trials from public budgets is politically difficult under current EU budget constraints. EU-harmonised pricing, reimbursement, and procurement mechanisms have in the past repeatedly met with MS resistance. A centralised pricing negotiation beyond the EU is even less realistic. Progress will therefore require incremental trust-building, demonstration projects in selected areas, and legal frameworks that balance national flexibility with cross-border collaboration. As a network of leading university hospitals across 10 MS and the UK, EUHA is committed to advancing these goals. Risks of hospital exemptions being misused for unsafe, unproven treatments highlight the need for stronger harmonisation and oversight.[22] At the same time, regulatory simplification must not compromise safety; safeguards should remain proportionate and avoid stifling innovation.

While regulatory and reimbursement frameworks pose hurdles, academic, non-profit, and SME ATMP developers must also strengthen their capacity to navigate them. Improving regulatory literacy through training and embedding regulatory science in research curricula, alongside specialised teams in academic and hospital centres, would support early alignment with EMA, HTA bodies, and national authorities. Stronger engagement, unified pharmacovigilance systems, and credible Risk Management Plans from the outset would help academic ATMPs progress more smoothly to clinical use while ensuring safety and quality.

In conclusion, EUHA calls for a future-proofed regulatory and financial ecosystem that fosters innovation, ensures patient safety, and promotes equitable access to ATMPs. In particular:

1 When MA is not possible (e.g. commercially not viable), EUHA supports the continued use of the Hospital Exemption (HE) scheme. We strongly support the case for a harmonised and cross-border use of HE.
2 For academic and non-profit developers of ATMPs, EUHA strongly supports the development of a support mechanism via a dedicated non-profit-organisation pathway to MA. This should include increased public funding for clinical trials and navigating regulatory procedures.
3 In those circumstances where the standard drug evaluation process is not possible, EUHA proposes a dedicated MA mechanism that includes use of Real-World Evidence. This pathway should include adaptive, dynamic designs of clinical trials and facilitated trial access for patients across the EU.
4 EUHA proposes innovative and EU-harmonised pricing, reimbursement and procurement solutions to be adopted by the EU and national frameworks once an ATMP becomes standard-of-care.

By engaging with the diverse stakeholders involved in this process to enact these changes, Europe can secure the promise of ATMPs for all patients, encourage continued scientific excellence, and build a healthcare ecosystem that transforms innovative science into real-world health outcomes available to all patients.

Contributors

Johan Van Eldere was involved in formulating the ideas, wrote the original draft, critically reviewed, revised, and edited the manuscript.

Annette Kunkele, Silvia Martin and Alessandro Aiuti were involved in formulating the ideas, critically reviewing, revising, and editing the orginal draft and the subsequent versions of the manuscript.

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