



IAP Statement on Regenerative Medicine

Regenerative medicine has great potential for tissue regeneration and repair, comprising various novel interdisciplinary approaches including the use of cell and gene therapies, and tissue engineering. The pace of advance in the science is exciting and the medical opportunities in addressing the causes of disease rather than the symptoms may be transformative, but concerns about the misuse of regenerative medicine technologies also grow.

Summary

In this consensus Statement the InterAcademy Partnership (IAP) seeks to raise awareness of two main priorities:

- To use advances in research and development as rapidly as possible, safely and equitably, to provide new routes to patient benefit.
- To support medical claims by robust and replicable evidence so that patients and the public are not misled.

The focus of this IAP Statement is on unmet medical needs: stem cells are described as a case study with many of our conclusions relevant more broadly

for regenerative medicine. Although stem cell therapy is well-established in only a limited number of clinical indications, there is active research and development in many more. However, enthusiasm about the clinical potential has led to a disconnect between expectations and the realities of translating advances in technology into clinical practice. In many countries, there are two main problems. First, unscrupulous private clinics offer unregulated therapies promising much, but using poorly characterised products with little scientific basis or evidence for efficacy, with safety concerns unresolved. Second, premature regulatory authority approval

and commercialisation based on some, but insufficient, scientific rationale and clinical evidence. Accelerated access is a vital tool for patient benefit but researchers must not cut corners.

In order to strengthen the frameworks for research and innovation and patient protection, IAP has identified priority actions for: engaging with patients, the public and policy makers; ethical assessment; pre-clinical and clinical research procedures; regulatory authorisation and options for facilitating access to new medicines; and noted the particular relevance of these actions also in the response to COVID-19.

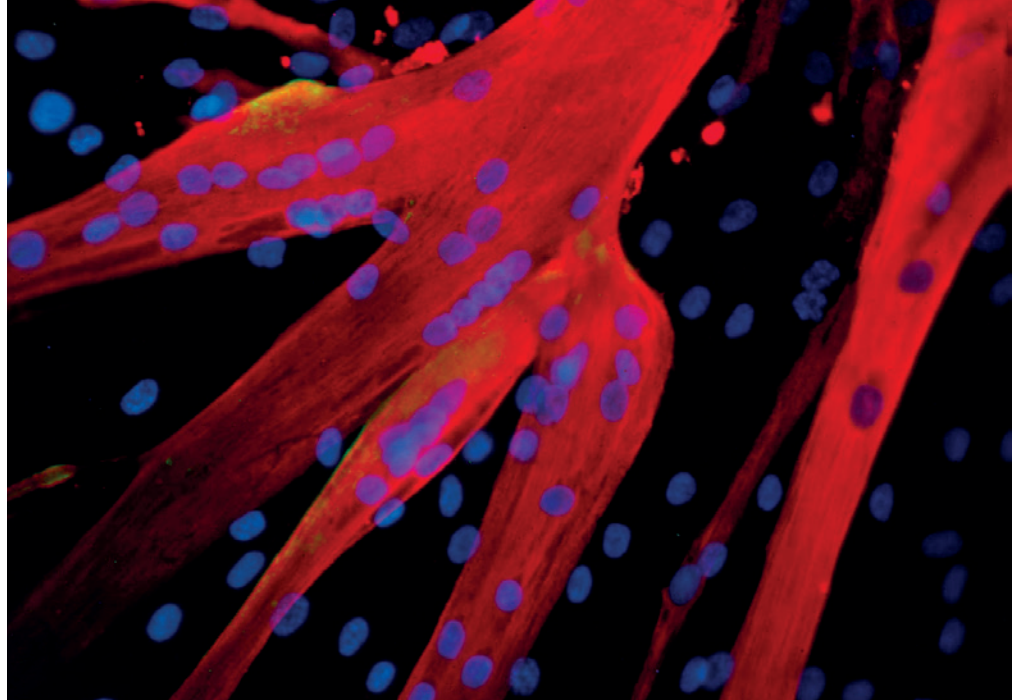
IAP concludes that:

- For the present, regenerative medicine should concentrate on serious medical conditions and be judged by rigorous consideration of the potential risks versus the benefits.
- For many potential applications, more evidence is needed on product quality, safety and efficacy.
- Good science must be promoted at every step, from fundamental research through to clinical trials and the translation to practice.
- Proportionate and harmonised regulatory authority actions should be based on robust and replicable science, ethically informed by science across the disciplines. Unregulated provision of unproven regenerative medicine must be deterred.
- Researchers must follow guidelines on responsible science, and teaching on regenerative medicine should be part of the curriculum for health professionals. Clinicians must be bound by both professional guidelines and community standards of medical practice.
- In putting patient interests first, the scientific and medical communities have a responsibility to provide reliable information and ensure that decisions are evidence-based.

Therefore, to deliver clinical benefits equitably, a coordinated strategy must encompass better science, better funding, better governance and better public and patient engagement.

Introduction

Regenerative medicine comprises various novel interdisciplinary approaches to healthcare, aimed at tissue regeneration, repair, restoration and reorganisation (Box 1). Regenerative medicine strategies



■ Muscle cells differentiated from human stem cells in culture, from ongoing research by Professor Giulio Cossu, University of Manchester, UK, on stem-cell therapy for muscular dystrophy.

depend upon harnessing, stimulating, guiding or replacing endogenous development and repair processes.

Purpose of this IAP Statement

The InterAcademy Partnership (IAP), the global network of more than 140 academies of science, engineering and medicine, is publishing this consensus Statement to build on the interest in regenerative medicine, and related issues for responsible science, expressed by members of academies and regional academy networks and to raise awareness of two main priorities for the field:

- To ensure that advances in science and innovation are used as rapidly as possible, safely and equitably, in providing new routes to patient benefit, potentially addressing the causes of disease rather than their symptoms.
- To ensure that medical claims are based on robust, replicable evidence

and that patients and the public are not misled, either deliberately or inadvertently.

The focus is on unmet medical needs. We address stem cells as a particular case study because of the urgent and complex challenges, but our conclusions can in most respects be generalised to other forms of regenerative medicine. We recognise that many other assessments have been made of this field but as the science is advancing rapidly and the commercial environment also changing rapidly it is timely and relevant now to provide global recommendations from the academies. We discuss principles rather than prescribe specific legislative actions and this IAP Statement is intended to inform and stimulate discussion with policy makers and regulatory authorities, our member academies and others in the scientific and medical communities more broadly. Some other international sources of information and analysis are listed in Box 2.

Box 1: The scope of regenerative medicine includes:

- Cell transplantation, where cells originate from human embryonic stem cells, perinatal stem cells, induced pluripotent stem cells or tissue specific (adult) stem cells or other forms of cell therapy
- Gene therapy, both *in vivo* and *ex vivo*, the latter being a form of cell therapy
- Tissue engineering, typically using 3D scaffolds formed from either natural biomaterials or artificial, biocompatible biomaterials produced from a variety of fabrication processes
- Organoids, from adult and pluripotent stem cells
- Small-molecule drugs
- Subcellular bodies (e.g. mitochondria, vesicles)
- Artificial cells (currently prokaryotic only) and other synthetic biology approaches

Identifying therapeutic opportunities and challenges

As noted in Box 1, regenerative medicine covers a wide range of approaches; even within the category of stem cells differing objectives are sought. Stem cell transplantation has a principal aim of replacing lost cells, requiring that the transplanted cells are committed to a specific fate and, once differentiated, are functionally integrated in the tissue. Alternatively, stem cells may provide

support for recipient cellular growth or differentiation via secreted products, mediate immunomodulation, or promote plasticity. Cell and gene therapies also have important roles in cancer treatment (e.g. chimeric antigen receptor T-cells) but here the main goal is to eliminate cancer rather than regenerate diseased tissue.

Regenerative medicine offers significant promise to tackle intractable diseases. Stem cell therapies are well established for bone marrow or epidermis transplantation, in congenital immunodeficiency, and lysosomal storage disease. In addition to the therapeutic applications, the methodologies of regenerative medicine, e.g. development of organoid models, are being used increasingly for *in vitro* assessment of biological function, evaluation of disease mechanisms and screening of novel pharmacological agents (Rowe and Daley, 2019).

Although stem cell therapy has proven itself, so far, in the treatment of only a limited number of approved clinical indications there is active research and development underway for many others, including neurological, hepatic, cardiovascular, retinal and musculoskeletal disorders¹. However, enthusiasm about the broad potential of regenerative medicine applications has led to a disconnect between expectations and the realities of translating technologies into clinical practice. To address this gap requires tackling multiple issues, for poor quality science, inconsistent ethical and regulatory policies, unclear funding models, unrealistic hopes and unscrupulous private clinics (Cossu *et al.*, 2018)², as outlined in the following sections. The consequences of not doing this would be to waste investment, researcher activity and aspirations to cure, as well as to undermine patient protection.

Box 2: International sources of information

Professional Societies: International Society for Stem Cell Research (ISSCR, www.isscr.org) and International Society for Cell & Gene Therapy (ISCGT, <http://isctglobal.org>) particularly for guidelines on research and development, and information for patients and other stakeholders. The ISCGT website provides recent updates on research for COVID-19 and on mesenchymal stromal cells and immune-mediated therapeutics. The ISSCR website provides recent support for enforced regulation of clinics offering unproven/unapproved interventions. TERMIS (<https://www.termis.org>), supporting the advancement of tissue engineering and regenerative medicine worldwide also provides much useful information as part of its remit to generate knowledge and improve patient outcomes.

EASAC and FEAM report (2020) for broad overview in Europe. See also *Lancet* Commission on Regenerative Medicine for discussion of opportunities and challenges (Cossu *et al.*, 2018) and NASEM (2019) for broad perspective on regenerative engineering products and their clinical translation. Other national academy work is described subsequently in the text (e.g. Ardaillou *et al.*, 2017).

European Medicines Agency (www.ema.europa.eu), providing various documents on advanced therapy medicinal products; concerns on unregulated products; accelerated access initiatives; good clinical practice. See also Hines *et al.* (2019) for future strategy. Many other national regulators provide relevant guidelines, e.g. in Japan (www.pmda.go.jp) the Pharmaceuticals and Medical Devices Act (2014), with conditional approval instituted for regenerative medicine in 2017, emphasises a focus on patient safety. The US Food and Drug Administration (www.fda.gov), provides guidance and warnings about unregulated products and initiatives on legal proceedings against providers. See also Marks and Gottlieb, 2018.

Alliance for Regenerative Medicine (<https://alliancerm.org>) particularly for information on products in development and issues for regulatory harmonisation.

Issues for supporting research and innovation while protecting patients

The pace of advance in regenerative medicine science is exciting and the medical opportunities are considerable, but the concerns also grow. We emphasise two major problems.

First, in many countries commercial clinics offer unregulated products and services promising a wide range of benefits using poorly characterised treatments with little or no evidence of efficacy, safety concerns, misleading scientific rationale, and with the

primary intention of financial profit. What principles and guidance should be available to inform patients contemplating such offerings?³ An informed patient should only consent to receiving stem cells (even if autologous) if the cell population is well-characterised, if clinical evidence on efficacy and side effects is well-documented, and if the number of patients treated previously with the same procedure is clearly disclosed. There is a crucial criterion for patients in deciding whether to consent: they should not be expected to pay to participate in clinical

¹ Recent scientific reviews of the current status of stem cells include De Luca *et al.*, 2019; Ntege *et al.*, 2020; and other sources cited by EASAC and FEAM, 2020. A recent update on industry developments is by Ilic and Liovic, 2020. Gene therapy is also a very active area of clinical research, mainly in cancer (melanoma, glioma) but approximately 10% of gene therapy trials focus on monogenic disease, see e.g. Mullard, 2019; Shahryari *et al.*, 2019. Future developments in regenerative medicine more broadly have been reviewed extensively elsewhere, e.g. Clarke *et al.*, 2018, NASEM, 2019.

² The opportunities and challenges for cell-based therapies are exemplified by a recent statement by the American Society of Bone and Mineral Research–Orthopaedic Research Society joint Task Force report (O’Keefe *et al.*, 2020), describing the potential to treat a range of disorders of the musculoskeletal system but also the possibility of misuse and misrepresentation for the efficacy of such treatment.

³ A recent account from the field of neurology in the USA observes that many neurologists are unprepared to discuss the issues surrounding stem cell therapies with their patients who seek advice about unproven offerings even though there are an alarming number of hitherto unreported complications from these unregulated procedures (Julian *et al.*, 2020). A standard for informed consent for stem cell-based interventions outside of clinical trials was published in 2019 by ISSCR, <https://www.isscr.org/docs/default-source/policy-documents/isscr-informed-consent-standards-for-stem-cell-based-interventions.pdf>.

research on regenerative medicine until it becomes an approved and consolidated treatment that may be reimbursed according to the specific procedures of each country health system, whether public or private.

Second, an evidence crisis occasioned by premature marketing approval and commercialisation of expensive approaches based on some, but insufficient, scientific rationale and clinical evidence, facilitated by regulatory authority initiatives for accelerated access. It is difficult to generalise because of a wide variation in researcher practices (EASAC and FEAM, 2020) but in some cases, the cells may be well characterised, protocols are registered with regulatory authorities, early results are published in reputable journals (that favour newsworthiness), yet the application for marketing approval is premature and based on inadequate evidence. Accelerated regulatory approval is an essential tool in bringing novel therapies to patients as fast as possible but it should not be abused by cutting corners in research and development. The problem persists despite the availability of international guidelines, e.g. from ISSCR.

In an era of increasing pressure for international competitiveness, where some regulatory frameworks become increasingly permissive (Sleeboom-Faulkner, 2019), it is essential that countries do not lower their regulatory threshold without fully considering the consequences for patient safety, healthcare budgets and public trust in science, and without ensuring that commitments on post-marketing studies are adhered to. Undesirable practices inherent in stem cell tourism are a consequence of the relative laxity in some national regulatory frameworks.

Academies have a continuing role to advise on priorities for research and innovation and can help to catalyse progress and monitor consistency of developments worldwide. These priorities include the following areas:

Ethical assessment

National regulatory conditions and clinical research frameworks are dependent on ethical considerations. Ethical issues must be addressed at various levels – including in health professional training and other education and as part of the approval and supervision of clinical trials, and should be based on interdisciplinary

perspectives, that is from social sciences as well as medicine, to take account of different expectations of medicines within and between different societies.

In addition to questions pertaining to safety and efficacy, the following ethical issues need to be addressed: patient expectations (is uncertainty about benefits outweighed for the patient by their lack of other options?); patient consent (can the patient understand the risk and benefit, is the intervention experimental, should the family be involved?); information (where can reliable advice be found?); professional responsibilities (might there be conflicts of interest?); and equity and fairness (do all patients have equal access and might limited health resources be diverted from other care?). However, regenerative medicine may not be within the competence of local ethical committees and then a case can be made for a national ethical committee.

Other ethical controversies in regenerative medicine have surrounded the provenance of donated biological samples and whether consent has been obtained, and the use of embryonic stem cells, although this latter concern is diminishing with the advent of induced pluripotency (where adult cells are de-differentiated to an embryonic stem cell-like state, although there will still be safety concerns if contaminated with undifferentiated cells which could develop into teratomas and tumours).

Clinical trial procedures and other research

As in other clinical areas, regenerative medicine trials should be performed according to an approved design, e.g. paying attention to expected recruitment numbers (recruiting the calculated minimum number, who may be exposed to unknown risks, necessary to obtain statistically significant results), standardised dosages, management of adverse effects, transparency in data collection, and criteria for premature termination of the trial. The clinical protocol should have been reviewed and approved by the host research organisation and by an ethics committee. There should be follow-up to collect data of failed as well as successful trials.

The implications of the orphan nature of some of the rarer clinical applications must be acknowledged in terms of designing clinical trials with an acceptable level of evidence for safety and efficacy. If patient groups

are small, it is difficult to conceive large, standard phase III placebo-controlled trials and there is more to be done internationally to facilitate a framework for robust evidence collection in these circumstances. One option for research capacity building globally is to focus on those initiatives, e.g. with haematopoietic stem cells, which may be relatively easier to establish in Low- and Middle- Income Countries (LMICs). However, adopting improved clinical trial procedures for other indications and other regenerative medicine approaches has significant implications for research infrastructure and for sharing skills worldwide.



Clinical research should be preceded by research *in vitro* and in animal models sufficient to provide a robust scientific foundation. This requires ensuring consistency in the composition and viability of the novel agent as it moves through successive stages of research and development. There are challenges in the scale-up from laboratory-level production to clinical and commercial scale and there must be attention to product quality throughout research and in the transition to industrial scale production (as recommended by a joint report from the French Academy of Medicine and Academy of Technologies, Ardaillou *et al.*, 2017).

More generally, there is a crucial role for investment in basic science and bioengineering to provide the resource for identifying next generation novel approaches and to inform scenario development. There is need for research in the social sciences on the ethical, legal and other societal consequences to support these longer-term considerations and to inform engagement with patient groups and others in civil society.



Regulatory authorisation and access to new medicines

Regulatory procedures need to become robust, transparent and evidence-based globally, without also becoming a heavy burden in terms of time and costs. Proportionate and consistent regulatory activities, including approval on the start of human studies, oversight of clinical trials, authorisation for marketing, post-marketing surveillance, and enforcement against fraudulent claims, must be based on replicable science. Unregulated provision of unproven regenerative medicine interventions must be deterred. The ethical issues and regulatory challenges need to be addressed in a rigorous, consistent and constructive way that includes the international development of standards⁴ as a step towards the necessary greater regional⁵ and global regulatory coordination (Qiu *et al.*, 2020). Harmonisation is important in making best use of the evidence base, but it does not solve the practical problem of unregulated, unscrupulous private clinics. A globally consistent framework might also introduce training and certification for practitioners of regenerative medicine and licensing

of permitted clinics once regulators authorise products.

Policy makers face difficult choices. The present systems of governance procedures are complex and there is variation in codes of conduct and other frameworks for regulating clinical research and development. Governments and intermediaries (such as universities) may have a vested interest in promoting regenerative medicine (McKelvey *et al.*, 2018). How should governance mechanisms be (re)designed to encourage enough risk-taking (experimentation) to develop radically new knowledge and innovation while at the same time protecting the safety of patients and protecting the population against misconduct and fraud? These are difficult challenges at the national level and even more difficult for international coordination.

Encouraging innovation while putting patients first requires action throughout research and development. For example, increasing investment in basic and clinical research must be accompanied by attempts to solve the problem of how expensive therapies can be reimbursed⁶ otherwise pipelines will

be filled with innovation that cannot be afforded. Health technology assessments and cost-benefit discussions, between the public and private sectors and with regulatory authorities, need to occur earlier in product development. Expensive therapies appear inequitable and equity is important for LMICs, indeed for all countries facing the very high prices that might be requested. However, it is necessary to take a long-term health economics approach: advanced technologies may bring sustained and substantial cost savings for an agent that initially appears cost-ineffective. If successful, a new therapy in regenerative medicine would eliminate costs of poorly efficacious existing therapies as well as the cost of assisting the patient, often for decades.

Engaging with patients, policy makers and the public

Notwithstanding the excellent work of professional scientific societies (Box 2), there is more to be done to create and share platforms to describe the difference between evidence-based practices and unproven, erroneous and illegitimate practices. As with other emerging technologies, better regulation and an informed public depend on education at all levels. Regulatory authorities and their advisers worldwide must have access to the latest biosciences/interdisciplinary experience. Education must encompass undergraduate and graduate programmes for health professionals and communication efforts with lay audiences and policy makers. Engagement worldwide should be sensitive to socio-economic context, literacy, religious and cultural beliefs.

IAP encourages its member academies and regional networks to become involved in the formulation of guidelines for research and practice; in discussion of the evidence base for claims of efficacy and safety; and in helping policy makers

4 For example, WHO (2020) describes ongoing work on the development of standards of cellular and gene therapy products to facilitate global convergence among regulators from both high-income countries and LMICs with regard to quality, safety, efficacy and post-market surveillance. The first proposed reference reagents are for pluripotent stem cell identity and mesenchymal stromal cell identity. See also Lee *et al.* (2017) for a discussion of possible additional WHO roles. While several international organisations are pursuing global standardisation, especially concerning cell banking, there is less harmonisation on assays for critical quality characteristics such as safety and potency (Karanu *et al.*, 2020).

5 An example of the measures involved in regional harmonisation that includes regenerative medicine is provided by the Task Force for Promoting Pharmaceutical and Medical Device Regulatory Harmonization in Asia (Executive Committee on Global Health and Human Security, 2020).

6 It is important for pricing negotiations to be more transparent and to be more clearly linked to costs of research and development and manufacturing: WHO discussions on transparency of health product markets (e.g. at the 72nd World Health Assembly in 2019) may help to stimulate action.

to decide on priority medical conditions (at a time when the boundary between medicine and biological enhancement may be increasingly diffuse, e.g. in preventing/retarding the effects of ageing). The focus in this IAP Statement on serious medical conditions is intended to cover a range of concerns that threaten health and interfere with the tasks of daily living as well as life-threatening conditions. The challenges in doing all this – with substantial implications for allocation of research and health care resources – are not, of course, confined to regenerative medicine, and have been explored in other IAP work⁷.

COVID-19

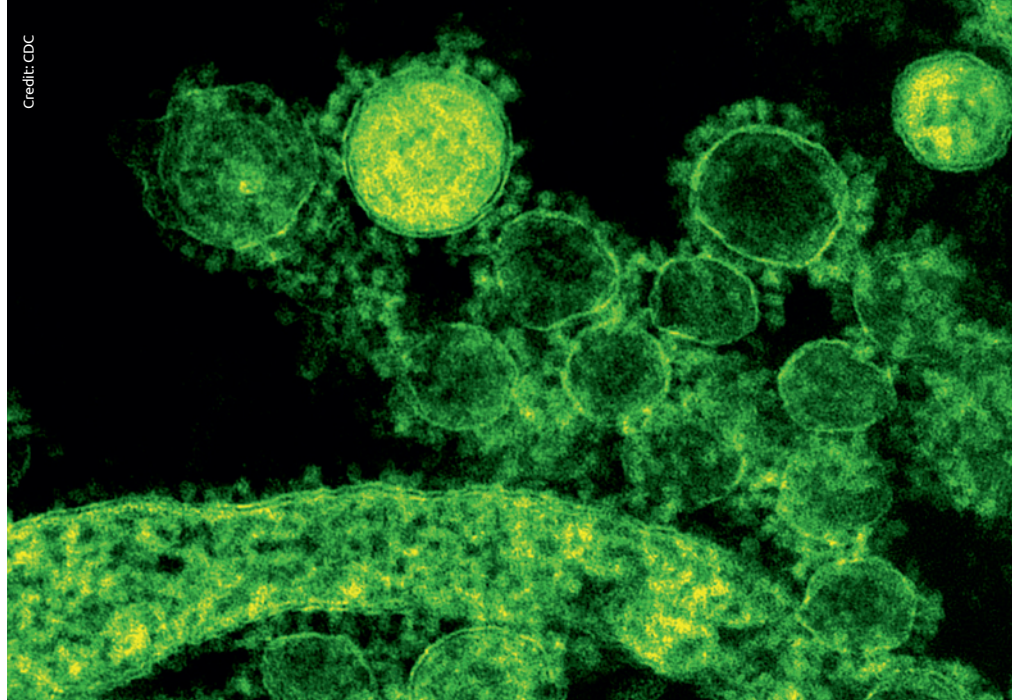
The points discussed above apply also to the proposed use of stem cells to tackle COVID-19. Any such use must be based on rigorous evidence of safety and efficacy, following strict research protocols that consider the ethical issues and characterise the stem cells used, focusing on a defined stage of the disease and in the hands of a team with capacity and validity to undertake the intervention.

Unfortunately, as the FDA observes, some of the same clinics in the USA that have been offering unproven regenerative medicine therapies for diverse conditions are now offering unproven treatments for the treatment of complications of COVID-19 (Marks and Hahn, 2020). There are other examples worldwide. While some research is in progress, e.g. on mesenchymal stromal cells, the preliminary studies are insufficient to support commercialisation. There is a further concern regarding these unproven treatments for COVID-19: fraudulent claims of efficacy may encourage purchasers to abstain from taking other steps, e.g. social distancing, to protect themselves and others from COVID-19.

IAP consensus recommendations

Regenerative medicine has transformative potential, but action is required from the scientific and policy communities to sustain responsible research and innovation worldwide, develop new forms of partnership, and build health services readiness while also engaging with patients and the public to counter misinformation and deter the

Credit: CDC



provision of unregulated interventions. Our key messages are:

- Regenerative medicine is designed to treat serious medical conditions with unmet needs, judged by rigorous consideration of the potential risks versus the benefits. Other applications are inappropriate for the time being.
- We are now at the threshold of being able to offer treatments for major genetic and other diseases – but for many, more evidence is needed on their likely benefit or efficacy, especially for the more complex polygenic and acquired degenerative diseases, and on safety, especially long-term safety.
- It is vital to promote good biomedical science – from fundamental research and its translation to clinical trials. This has implications for public sector commitment to funding of well-planned first-in-human trials with reliable, shared and objective end-points determined with input from supporting expert networks and patients. There are also implications for novel forms of partnership between academia and industry and with regulatory agencies.
- Proportionate and consistent regulatory activities must be based on robust and replicable science, ethically informed by science across the disciplines, and accompanied by efforts for international harmonisation. Unregulated provision of unproven regenerative medicine procedures must be deterred.
- Researchers must follow professional guidelines on responsible research (both in pre-clinical and clinical phases) and standard-setting, in pursuit of good practice. Clinicians must be bound by both professional guidelines and community standards of medical practice.
- Teaching on regenerative medicine should be part of the curriculum for health professionals.
- Scientific and medical communities have a responsibility to provide reliable sources of information and ensure that discussions and decisions are evidence-based. The risks created by misinformation go deeper than the possible harms to individuals. There is also potential to harm the credibility of research and scientific integrity.
- Patient interests must be put first. There must be a validated scientific basis for the clinical intervention and for the end-points selected for measurement of efficacy and safety, as well as a commitment to share good practice internationally.

In summary, in order to deliver sustainable, clinically significant and equitable benefits from regenerative medicine, a coordinated strategy needs to encompass better science, better funding, better governance and better public and patient engagement. Academies worldwide are ready to play their part at the national, regional and global levels.

⁷ For example. IAP with UK Academy of Medical Sciences 2019, 'Achieving universal health coverage in LMICs: the role of quality of care research'; IAP co-signatory in open letter to the UN, 2020 'Health inequity during the pandemic: a cry for ethical global leadership.'

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Academies that have endorsed the Statement on Regenerative Medicine (July 2021)

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The InterAcademy Partnership

Under the umbrella of the InterAcademy Partnership (IAP), more than 140 national, regional and global member academies work together to support the vital role of science in seeking evidence-based solutions to the world's most challenging problems. In particular, IAP harnesses the expertise of the world's scientific, medical and engineering leaders to advance sound policies, improve public health, promote excellence in science education, and achieve other critical development goals. Statements such as this one are prepared by a working group comprising experts nominated by member academies, and are released once they have been endorsed by more than half the member academies of the network.

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