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1 **Innovative regenerative medicines in the EU: a better future in evidence?**

2

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23

## 24 **Abstract**

## 25 **Background**

26 Despite a steady stream of headlines suggesting they will transform the future of healthcare,  
27 high-tech regenerative medicines have, to date, been quite inaccessible to patients; only eight  
28 have been granted an EU marketing licence in the last seven years. Here, we outline some of  
29 the historical reasons for this paucity of licensed innovative regenerative medicines. We  
30 discuss the challenges to be overcome to expedite the development of this complex and  
31 rapidly changing area of medicine, together with possible reasons to be more optimistic for  
32 the future.

## 33 **Discussion**

34 Several factors have contributed to the scarcity of cutting-edge regenerative medicines in  
35 clinical practice. These include the great expense and difficulties involved in planning how  
36 individual therapies will be developed, manufactured to commercial levels, and ultimately  
37 successfully delivered to patients. Specific challenges also exist when evaluating the safety,  
38 efficacy and cost-effectiveness of these therapies. Furthermore, many treatments are used  
39 without a licence from the EMA - under “Hospital Exemption” from the EC legislation. For  
40 products which *are* licensed, alternative financing approaches by healthcare providers may be  
41 needed, since many therapies will have significant up-front costs but uncertain benefits and  
42 harms in the long-term.

43 However, increasing political interest and more flexible mechanisms for licensing and paying  
44 for therapies are now evident. These could be key to the future growth and development of  
45 regenerative medicine in clinical practice.

## 46 **Conclusions**

47 Recent developments in regulatory processes, coupled with increasing political interest may  
48 offer some hope for improvements to the long and often difficult routes from laboratory to  
49 marketplace for leading-edge cell or tissue therapies. Collaboration between publicly-funded  
50 researchers and the pharmaceutical industry could be key to the future development of  
51 regenerative medicine in clinical practice; such collaborations might also offer a possible  
52 antidote to the innovation crisis in the pharmaceutical industry.

53

54 Keywords: Regenerative medicine, European Medicines Agency, cell therapy, gene therapy

55

## 56 **Background**

57 '*Cure for blindness found*' proclaimed a front page headline of a UK newspaper.[1] The  
58 article's text revealed a different story, of a promising line of research based on clinical trial  
59 data from just a single patient treated with an embryonic stem cell therapy, for which it 'will  
60 be some months before the full impact of it [the treatment] on her sight is known'. Although  
61 the fullness of time may yet reveal this new treatment to be a cure for blindness, this example  
62 illustrates the weight of expectation often placed on innovative new 'regenerative medicines'  
63 to transform the future of healthcare. Regenerative medicine - which is not a new field of  
64 medicine as it encompasses bone marrow or organ transplants - deals with the process of  
65 replacing or regenerating human cells, tissues or organs to restore or establish normal  
66 function.[2] Most new regenerative medicines will be classed by the European Medicines  
67 Agency (EMA) as being 'advanced-therapy medicinal products' (ATMPs) which are  
68 *engineered* regenerative medicines, and which encompass cell-based therapies (often using

69 stem cells or progenitor cells to produce tissues), gene therapies, and tissue-engineered  
70 therapies.

71 The Committee for Advanced Therapies (CAT) is the EMA committee responsible for  
72 assessing the quality, safety and efficacy of ATMPs (and for following scientific  
73 developments in the field). Several EMA regulatory pathways exist which facilitate  
74 accelerated access to treatments where there is unmet patient need. These include: approval  
75 under exceptional circumstances (1993), conditional marketing authorisation (2005),  
76 accelerated assessment (2005), parallel scientific advice between EMA and FDA (2009) and  
77 the adaptive licensing pilot programme (2014). However, only eight ATMPs have been  
78 granted a marketing licence by the EMA: ChondroCelect (2009), Glybera (2012), MACI  
79 (2013), Provenge (2013), Holoclar (2015), Imlygic (2015), Strimvelis (2016) and Zalmoxis  
80 (2016), yet 318 relevant trials were performed in Europe between 2004 and 2010. The main  
81 sponsors were academic organisations, charities, and small companies - stakeholders who  
82 tend to have limited resources with regard to both financing and the capacity to navigate the  
83 required regulatory procedures.[3] This mismatch between the number of promising ideas  
84 and translation to actual patient benefit[4] may partly be due to key differences between  
85 regenerative medicines and conventional pharmaceuticals. Regenerative medicines are often  
86 truly personalised and therefore expensive and difficult to manufacture; evaluation of their  
87 efficacy, safety and cost-effectiveness may also be challenging.[5, 6]

88 Nevertheless, there appears a new sense of urgency to address these issues. In the UK, a  
89 House of Lords Science and Technology Committee inquiry into regenerative medicine  
90 identified barriers to translation and commercialisation and recommended solutions. In  
91 response to its findings - published in 2013 - the National Institute for Health and Care  
92 Excellence (NICE) was asked to commission a study to assess whether its current appraisal  
93 methods and processes were appropriate to evaluate regenerative medicines. We were part of

94 the team which performed that study, which included an assessment of previous evaluations  
95 of regenerative medicines by NICE, the EMA and the Food and Drug Administration  
96 (FDA).[7, 8] More recently (in April 2016), the House of Commons Science and Technology  
97 Committee announced it was undertaking an inquiry into regenerative medicine, which will  
98 report in early February 2017. In this article we discuss some of the historical causes for the  
99 scarcity of licensed innovative regenerative medicines, together with possible reasons to be  
100 more optimistic for the future. This paper arose as a result of our work on the aforementioned  
101 study for NICE which was commissioned by the Regenerative Medicine Expert Group.

## 102 **Discussion**

### 103 **The evidence-access trade-off**

104 Although the randomised controlled trial is the expected level of evidence for regulatory  
105 assessments, it is likely that many evidence submissions for regenerative medicines will  
106 comprise small, single-arm, short-term, early phase clinical trials. These sub-optimal study  
107 designs are likely to produce biased and imprecise results. However, the use of such designs  
108 is not inevitable and is unlikely to be through choice, but is instead a consequence of the type  
109 of patients targeted by new therapies. Populations with rare, severe or advanced disease may  
110 be very small, so adequate recruitment to trials with two treatment arms would require many  
111 centres, much time, and great expense. Also, where no alternative treatments exist, and  
112 patients have life-threatening or severe disease, randomisation to a control group is likely to  
113 be ethically unacceptable or problematic, as may the requirement for lengthy follow-up  
114 before licence submission. This is particularly likely to be a problem when initial studies on  
115 small numbers of patients have shown spectacular results.[9] Trials utilising alternative  
116 approaches to conventional randomisation might also be considered when rare diseases are  
117 studied.[10] For example, responsive-adaptive randomisation maximises allocation to the

118 most effective treatment and minimises the required sample size. Such a 'play the winner'  
119 design has the potential to reduce the number of patients allocated to less effective treatment  
120 therefore reducing the ethical concerns associated with randomisation, though it is limited to  
121 studies which assess rapidly available outcomes. However, for new types of study design  
122 such as this, the magnitude of the risks of bias are not yet well understood;[11] in reality  
123 single-arm studies are therefore most likely to be submitted for licensing purposes.

124 Another issue often encountered is the use of surrogate endpoints - laboratory or  
125 physiological measures used to predict or provide an early measure of therapeutic effect -  
126 rather than real clinical (patient-important) endpoints. Surrogate endpoints data are quicker  
127 and easier to acquire than real clinic endpoint data, thus saving valuable time in the licensing  
128 process (for both manufacturers and patients) However, there is often considerable  
129 uncertainty about the strength of the relationship between a given surrogate and its relevant  
130 real clinical endpoint; this is problematic because trial results based on surrogate endpoints  
131 are not likely to be reliable if the surrogate has not been properly validated. It is therefore  
132 recommended that before a surrogate outcome is accepted, a systematic review should be  
133 conducted examining the evidence for the validation of the surrogate-final outcome  
134 relationship. To validate a surrogate endpoint such reviews must demonstrate there is  
135 adequate evidence from several sources: clinical trials, epidemiological/observational studies  
136 and pathophysiologic studies (of biological plausibility of the relationship).[12]

137

138 Also, for those treatments studied in very specialised settings, scepticism about results may  
139 arise from evidence suggesting that single-centre trials tend to produce significantly larger  
140 effect estimates than multi-centre trials. A systematic review of 82 critical care medicine  
141 RCTs found significantly larger treatment effects for all-cause mortality in single-centre trials  
142 when compared with multi-centre trials (ratio of odds ratios, 0.64; 95% CI 0.4, to 0.87).[13]

143 Where ATMPs are likely to be delivered from more than just a single clinic site, efficacy  
144 results from single-centre trials should be considered cautiously by decision makers.

145

146 The implications of such evidential problems will largely depend on both the level of unmet  
147 need in the studied population and the likeliness of cure or improvement *without*  
148 experimental treatment. This can be illustrated by comparing two quite recently licensed  
149 therapies which claimed to meet unmet patient needs: Holoclar (a stem cell-based therapy for  
150 treating corneal lesions resulting from burns to the eye) and Glybera (a gene therapy for  
151 treating familial lipoprotein lipase deficiency with associated pancreatitis). It seems Holoclar  
152 and Glybera had very different approval histories primarily due to differences in the  
153 likelihood of patient improvement without new therapy. Despite the clinical evidence for  
154 Holoclar being based on uncontrolled retrospective data, the results - around half the patients  
155 had improved visual acuity - were still sufficiently impressive for the EMA to grant a  
156 conditional licence on the first application. The prospective confirmatory study required as  
157 part of the EMA's conditional approval should clarify Holoclar's efficacy and safety.

158

159 The application for Glybera was also supported by single-arm trial evidence. But while the  
160 evidence for Holoclar was deemed sufficiently robust, for Glybera there were concerns that  
161 the apparent treatment benefit may have been due to chance, resulting in Glybera's long and  
162 protracted route to marketing authorisation. Negative committee opinions were issued in June  
163 2011, with approval finally granted in July 2012 with a more restrictive licence than was  
164 originally applied for. In 2015 the manufacturer of Glybera dropped plans to seek approval  
165 for the therapy in the U.S. following the FDA's request for further clinical data.

166



167 As outlined earlier, the EMA has several regulatory pathways which attempt to create a  
168 balance between shorter approval times for promising medicines for populations with high  
169 unmet medical need, and ensuring a flow of evolving satisfactory information on efficacy and  
170 safety. The most recent update - the adaptive pathways pilot programme - utilises existing  
171 regulatory processes, and is a prospectively planned adaptive approach to bringing treatments  
172 to market with an initial focus on patients with high unmet need. It will be more of a  
173 staggered, iterative system than previous approval pathways. Such a ‘life-cycle approach’ to  
174 acquiring and (re)assessing evidence will consider the basis of decision making in the  
175 following stages of a product’s life cycle: development, licensing, reimbursement,  
176 monitoring/post-licence evidence and utilisation.[14, 15]

177 Improvements to this life-span approach are developing at pace. For example, with MAPPs  
178 (Medicines Adaptive Pathways to Patients) the development plan across target populations  
179 and indications will be agreed up-front with the EMA. Plans may include a range of studies,  
180 such as RCTs, single-arm studies, pragmatic trials and other forms of real world study.[16] A  
181 newly formed public-private project called ADAPT SMART (Accelerated Development of  
182 Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to  
183 Treatment-outcomes), funded by the EU Innovative Medicines Initiative, is focused on laying  
184 the foundations for MAPPs to be put into practice in Europe. The challenge for ADAPT  
185 SMART is to develop an approach to adaptive pathways that aligns the needs of all  
186 stakeholders, including patients, member state payers, regulators, medical practitioners and  
187 industry.[17] Finally, the recent proposals for developing a more enabling environment for  
188 ‘strategically important transformative products’ that the UK Department of Health (2016)  
189 has announced is regarded as an additional vehicle through which ATMPs might be fostered.  
190 Crucial to this will be the establishing of ‘accelerated access partnerships’ between public

191 and private sectors and the NHS of a form not seen before, suggesting that its success will  
192 depend as much on identifying transformative processes as much as products.[18]

### 193 **Development of ideas and scale-up to commercialisation**

194 Most new regenerative medicines are developed by academic research institutions or small-  
195 and medium-sized enterprises. Ideas for new therapies are not uncommon, but it is difficult  
196 for new centres to enter the field under existing regulations; producing regenerative  
197 medicines in accordance with good manufacturing practices - to ensure quality, safety and  
198 efficacy - is expensive and the ongoing costs are frequently overlooked by academic centres  
199 with no history of cell therapy manufacture. Successful academic centres are often those with  
200 pre-existing quality management systems and staff experienced in manufacturing more  
201 conventional cell therapy products (e.g. those relating to haematopoietic stem cell  
202 transplantation and lymphocyte infusion).[19]

203 The wide variation evident across the types of new cell-based medicines[20] highlights the  
204 importance of careful consideration of how individual therapies will be developed,  
205 manufactured, and ultimately successfully delivered to patients in clinical practice settings to  
206 commercially viable levels. Key differences in issues will also arise depending on which of  
207 the two main types of cell is being used when developing a new therapy: autologous  
208 (bespoke) cell therapies, which are derived from an individual patient's own cells and  
209 allogeneic (universal) cell therapies which are derived from a donor. A clear understanding of  
210 what will be needed for scale-up to commercial levels is particularly important. Autologous  
211 therapies have advantages over allogeneic therapies in terms of: smaller start-up costs,  
212 simpler regulations, the potential for point-of-care processing, and ease of obtaining cells (in  
213 terms of time and resources). Allogeneic therapies have advantages over autologous therapies  
214 in terms of: patient throughput, product consistency, quality control being applied to larger  
215 lots, and treatment delays from processing failures.[21] Of the eight ATMPs licensed to date,

216 five have been autologous, two have been viral gene therapies (Glybera and Imlygic) and one  
217 allogeneic (Zalmoxis).

218 The Cell and Gene Therapy Catapult is an organisation dedicated to growing the UK cell and  
219 gene therapy industry by bridging the gap between academic research and full scale  
220 commercialisation. It promotes and develops the existing early phase manufacturing network;  
221 the UK's small-scale academic facilities are a good source of materials for early-stage clinical  
222 trials although they are expected to reach full capacity within a few years as the industry  
223 matures. With this in mind, the Catapults' work will be augmented by a £55m large-scale  
224 manufacturing facility (due to open in 2017).[22] The centre aims to provide an infrastructure  
225 to enable the manufacture of allogeneic or autologous cell therapies for later phase (II or III)  
226 clinical trials and commercial scale-up. For developing businesses this will mean that  
227 finances need not be committed to a permanent commercial facility before it is known  
228 whether products are going to be both clinically useful and economically viable. The vision is  
229 that successful products will eventually be manufactured from purpose-built facilities  
230 operated by successful firms. Input from organisations such as the Cell and Gene Therapy  
231 Catapult could be crucial – company size appears to be an independent predictor of outcome  
232 of a marketing authorization application to the EMA: the smaller the company, the more  
233 likely a negative outcome. Direct interaction with regulators also appears to be a key  
234 predictor of success.[23]

### 235 **Reimbursement by healthcare systems and evaluation of cost-effectiveness**

236 How should we value and price therapies which might cure chronic or fatal diseases? How  
237 should we pay for them? Claims of long-term benefits (perhaps even cures), long-term safety  
238 issues due to persistence of therapeutic cells, and significant up-front costs are issues which  
239 raise particular challenges in the assessment of the cost-effectiveness of regenerative  
240 medicines. Even where there may be significant potential benefits over current therapies,

241 these may not be known with a high level of certainty at the time of licensing.[7, 8]  
242 Furthermore, a key difference between regenerative medicines and conventional medicines is  
243 the possibility that therapies may change over time. For example, when the ATMPs MACI  
244 and ChondroCelect (treatments for knee cartilage defects) were assessed by NICE they were  
245 third generation products. This may pose further uncertainty problems since by the time long-  
246 term trial results become available, the particular studied therapy may well have been  
247 superseded by a (*apparently* superior) next-generation treatment.

248 For EMA licensing purposes a sponsor must demonstrate a favourable benefit-risk balance.  
249 However, the level of evidence required to achieve this can be less than that needed to  
250 estimate the relative effectiveness compared to current practice, or to quantify long-term  
251 treatment benefits. Since this latter information is essential for reliable assessment of cost-  
252 effectiveness, developers may find it is more difficult to demonstrate cost-effectiveness for  
253 reimbursement than it is to demonstrate efficacy for licensing. Schemes that allow  
254 development of further evidence or entail a risk-sharing component (between the payer and  
255 the manufacturer) may therefore be required.

256 Managed entry agreements (MEAs) or performance-based risk sharing agreements (PBRsAs)  
257 are an increasingly common policy response for dealing with evidence base uncertainty.  
258 PBRsAs involve the performance of treatments being tracked in a defined patient population  
259 over a specified time period, with the level or continuation of reimbursement based on the  
260 health and economic outcomes achieved. PBRsAs fall under a variety of names and  
261 categories: outcomes-based schemes, risk-sharing agreements, coverage with evidence  
262 development, access with evidence development, conditional licensing and managed entry  
263 schemes. Patient access schemes (PASs) may also sometimes be linked to performance.  
264 There has always been much uncertainty about the ultimate real-world clinical and economic

265 performance of new products; PBRsAs represent one mechanism for reducing this  
266 uncertainty.[24]

267 Concern surrounding the potential high up-front costs of regenerative medicines and their  
268 affordability to health care systems means that alternative financing approaches may also  
269 have to be considered. These include pay for performance, where the total price is more  
270 directly related to therapy performance in clinical practice, and amortisation, where payments  
271 are spread over the expected duration of benefits.[25] The appropriateness of employing  
272 different discount rates and/or different rates over time is also an area requiring careful  
273 consideration, particularly for potentially curative therapies.

274 Successful adoption of newly licensed ATMPs may well depend on how they relate to  
275 existing clinical interventions. The manufacturer of ChrondroCelect - a licensed treatment for  
276 knee cartilage defects - recently announced the initiation of the withdrawal of marketing  
277 authorisation due to commercial reasons. The EMA's marketing authorisation for MACI  
278 (also a therapy for knee cartilage defects) was suspended in September 2014 as an authorised  
279 manufacturing site no longer existed (the developer closed the site). A key issue here could  
280 be the availability of alternative, more cost-effective treatments: established treatments such  
281 as microfracture have long been available for repairing knee cartilage defects. More recently,  
282 in December 2016, the FDA gave marketing authorisation to MACI in the USA, and Vericel  
283 will now try to build a new market for this there. ATMPs are likely to be expensive and these  
284 examples suggest they may be most likely to succeed commercially where there is an unmet  
285 medical need.

## 286 **Remaining hurdles and uncertainties**

287 Despite some reasons to be more optimistic about the future of regenerative medicine, further  
288 challenges abound. One important issue is that many therapies are currently used without a

289 licence from the EMA under “Hospital Exemption” from the EC legislation (or via the  
290 “Specials” scheme in the UK). Such treatments are prepared on a non-routine basis according  
291 to specific quality standards and are used for individual patients in a hospital under the  
292 professional responsibility of a medical practitioner. The problem is that hospital exemptions  
293 are regulated at the national level, with different countries interpreting the legislation in  
294 different ways; harmonisation and clarity are needed in defining when treatments qualify.  
295 There is concern about a risk that a too broad use of hospital exemptions may deter the  
296 submission of marketing authorisation applications to the EMA.[26]

297 Careful consideration of longer-term adverse effects profiles is also important, as they may  
298 not be straightforward. While many harms associated with pharmaceuticals may improve  
299 following discontinuation, for regenerative medicines there is the possibility of prolonged  
300 harms, especially where cells persist long-term. Developing effective methods for inducing  
301 immune tolerance of allogeneic therapies also remains a challenge. Patients receiving  
302 allogeneic cells may need long-term immune suppression to avoid rejection. More broadly,  
303 concerns have been raised that the evidence for benefits to patients of adaptive pathway  
304 approaches is lacking or contradictory.[27] There is also concern about the follow-up  
305 evidence for some treatments granted conditional approval by the EMA, with inconsistencies  
306 and delays in the fulfilment of specific obligations.[28, 29]

307 The optimum approach for manufacturing autologous therapies is likely to be difficult to  
308 predict. Autologous therapies can be manufactured centrally although an example of the type  
309 of difficulties encountered with some centralised production models is provided by  
310 considering Provenge (sipuleucel-T), a cell-based immunotherapy for treating prostate  
311 cancer. The process involved patient cells being cold-shipped to a manufacturing site, where  
312 target immune cells were isolated and activated. These were then cold-shipped back to the  
313 patient, re-infused and the process repeated three times. The product handling and

314 manipulation was mostly manual which led to high product operating costs. Although efforts  
315 were made to reduce costs by automating some process stages, this example highlights the  
316 importance of considering functionally closed and automated scale-out processes early in  
317 clinical development.[30] In May 2015 the EU marketing authorisation for Provenge was  
318 withdrawn at the request of the manufacturer for commercial reasons.

319 An alternative approach to producing autologous therapies centrally is scaling-*out*, rather than  
320 scaling-up (in a large facility). Historical successful examples of the creative use of existing  
321 multiple centres with technically-advanced facilities include organ, bone-marrow and stem-  
322 cell transplants.[31] However, achieving a high level of product quality with decentralised  
323 models requires highly standardised, robust and transparent manufacturing processes and  
324 platforms.[32] In-hospital micro-factories are also prominent, particularly for autologous  
325 procedures that entail significant surgery/patient contact. Current examples include limbal  
326 stem cell transplantation and the bioengineered trachea. Nevertheless, whether multiple  
327 hospitals will be willing or able to commit to good manufacturing practice (GMP) under  
328 licence is untested. The UK moves towards ‘Cell and Gene Therapy Treatment Centres’ as  
329 recommended by the Advanced Therapies Manufacturing Taskforce (2016) poses new  
330 challenges for hospitals and the clinical science system more generally in designing new  
331 treatment infrastructures – with specific skills set, logistical and equipment demands and  
332 regulatory oversight – for ATMPs.[33] Centralised production of autologous therapies may  
333 be seen as more appropriate, as is currently happening with a therapy (CTL019) being  
334 developed by Novartis; CTL019 is one of a number of CAR (chimeric antigen receptor) T-  
335 cell blood cancer therapies.

336 Providing a good illustration of many of the issues raised in this article, CAR T-cell therapies  
337 are a regenerative medicine to watch out for in the near future. They may offer a potential

338 cure for very ill patients with high unmet medical needs - typically patients with  
339 refractory/relapsed leukaemia - though they have potentially serious adverse effects.

340 In autologous CAR T-cell therapies a patient's T-cells are genetically modified whereby the  
341 activated T-cells can attack and destroy leukaemia B-cells. These therapies have been under  
342 development for around 20 years, they are truly innovative and they have received much  
343 press attention due to very encouraging early phase trial results.[7] Such results mean that use  
344 of a randomised controlled design in further trials would not be ethical in the patient  
345 populations being studied.

346 CAR T-cells are costly and complex to produce. For Novartis's CTL019 the initial work was  
347 carried out in an academic setting with the treatments now being produced in centralised  
348 large scale facilities. This is in preparation for licensing trials and marketing authorisation.  
349 Interestingly, in terms of the viability and cost-effectiveness of manufacture, CTL019 is  
350 being produced in the same facility as (the aforementioned) Provenge was. However, there  
351 appear to be key differences between these therapies: the benefits from CTL019 seem likely  
352 to be much greater than those from Provenge and CTL019 is frozen-shipped, so  
353 transportation and timing issues should be minimised. Novartis bought the facility from  
354 Dendreon, the biotech company which used to manufacture Provenge.

355 The CAR T-cell example also highlights the importance of adequately robust research both  
356 for marketing authorisation *and* beyond. When to treat with CAR T-cells, what pre-  
357 conditioning is needed, and how to manage toxicity due to cell persistence are just some of  
358 the issues which will need resolving.



## 359 **Conclusions**

360 Notwithstanding some challenges, the EMA’s recent approval of Strimvelis and the  
361 conditional approval of Holoclar provide examples of successful collaboration between  
362 publicly-funded researchers and the pharmaceutical industry.[34, 35] Such collaborations  
363 could be the antidote to the innovation crisis in the pharmaceutical industry, where much  
364 research is aimed at developing safe-bet “me too” drugs which offer little or no benefit over  
365 treatments already available.[36] Collaboration may allow closer attention to the patient  
366 pathway and reduce time to market by ensuring more straightforward adoption into clinical  
367 practice.[37]

368 The more flexible regulatory landscape, more appropriate range of options for reimbursement  
369 and increasing political interest and support structures do *suggest* a brighter future for  
370 regenerative medicine - the licensing of four ATMPs between 2015 and 2016 attest to this.  
371 Nevertheless, only time will tell as to whether future ‘cure for blindness’ headlines reflect the  
372 probable, rather than the possible.

373

## 374 **List of abbreviations**

375 ADAPT SMART Accelerated Development of Appropriate Patient Therapies: a Sustainable,  
376 Multi-stakeholder Approach from Research to Treatment-outcomes

377 ATMP advanced-therapy medicinal product

378 CAR chimeric antigen receptor

379 CAT Committee for Advanced Therapies

380 EMA European Medicines Agency

381 FDA Food and Drug Administration

382 GMP Good manufacturing practice

383 MEA Managed entry agreement

384 MAPPs Medicines Adaptive Pathways to Patients

385 NICE National Institute for Health and Care Excellence

386 PBRsAs performance-based risk sharing agreements

387 PASs Patient access schemes

388

389 **Declarations**

390 **Ethics approval and consent to participate:** Not applicable

391 **Consent for publication:** Not applicable

392 **Availability of data and materials:** Not applicable

393 **Competing interests:** MC, NW and AW have no competing interests. RH is a

394 shareholder/founder of Cellular Therapeutics Ltd (CTL) which is a contract manufacturer

395 which makes autologous products for academic or commercial groups. RH has received

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400 coordinated the authors' comments. RH and AW provided expert advice. NW, RM and AW  
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405 commissioned by the Regenerative Medicine Expert Group (the group was established by the  
406 Department of Health). The 2015 study assessed whether NICE's appraisal methods and  
407 processes were appropriate to evaluate regenerative medicines (see reference 7). MC and  
408 NW were co-authors of that study. RH and AW provided expert advice during the study. AW  
409 is PI on a related ESRC-funded project REGenableMED which also informed the paper.

410 **Figure legends:** Figure 1: Overview of key stages and associated issues when bringing an  
411 ATMP to market in the EU

412

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