Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

KEYNOTE (GREEN)

The impact of COVID-19 on the cell and gene therapies industry: Disruptions, opportunities, and future prospects

Tingting Qiu, Yitong Wang, Shuyao Liang, Ru Han, Mondher Toumi *

Department of Public Health, Aix-Marseille University, Marseille, France

Coronavirus 2019 (COVID-19) has caused significant disruption to the cell and gene therapy (CGT) industry, which has historically faced substantial complexities in supply of materials, and manufacturing and logistics processes. As decision-makers shifted their priorities to COVID-19-related issues, the challenges in market authorisation, and price and reimbursement of CGTs were amplified. Nevertheless, it is encouraging to see that some CGT developers are adapting their efforts toward the development of promising COVID-19-related therapeutics and vaccines. Manufacturing resilience, digitalisation, telemedicine, value-based pricing, and innovative payment mechanisms will be increasingly harnessed to ensure that market access of CGTs is not severely disrupted.

Keywords: COVID-19; Cell and gene therapies; Regulatory; Health technology assessment

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused global damage to livelihoods and health since it was first reported in Wuhan, China, in late 2019 [1]. To date (17 March, 2021), there have been 120,667,101 confirmed cases and 2,670,274 people have died from COVID-19 worldwide [2]. The scale and severity of COVID-19 are unprecedented, and it has significantly disrupted social, economic and political activities worldwide. The pharma industry, similar to other key economic sectors, has been severely disrupted as a consequence. This disruption has been particularly damaging for the cell and gene therapies (CGTs) industry, because of its complexities in manufacturing, supply chains, and clinical trials, in addition to the substantial challenges in price, reimbursement and market access [3]. However, the COVID-19 pandemic has also provided opportunities for the pharma industry, especially because of the need for a 'miracle' drug and vaccines to combat COVID-19. CGT companies, with their extensive experience in cell biology, cellular immunity, genomic technol-

Tingting Qiu is a PhD student at Aix-Marseille University, France, majoring in public health. She has been involved in projects concerning expensive drugs (e.g., orphan drugs and advanced therapies) on the European market since 2017, such as health policy research, value proposition proposal, business model strategy, and expert interviews. She has a MSc in clinical pharmacy from China Pharmaceutical University, and has experience in clinical evidence synthesis and patient education.

Mondher Toumi has an MD and MSc in biostatistics and in biological sciences (option pharmacology) and a PhD in economic sciences. He is professor of public health at Aix-Marseille University, France. He is also the founder of CreativCeutical, an international consulting firm dedicated to supporting health industries and authorities in strategic decision-making. He also created the European Market Access University Diploma (EMAUD). He is a recognised expert in health economics and an authority on drugs market access and risk management.

* *Corresponding author.* Toumi, M. (Mondher.Toumi@emaud.eu)

https://doi.org/10.1016/j.drudis.2021.04.020

ogy, and viral vector manufacturing, could have specific advantages in researching and developing promising therapeutics for COVID-19.

In this review, we first discuss how the COVID-19 pandemic has caused disruption to the overall activities of CGT development, from manufacturing through to health technology assessment (HTA) and reimbursement. In addition, we discuss progress made during the pandemic in terms of potential CGTs for COVID-19-related disorders, finances raised for continued development, and CGTs that have been newly launched for non-COVID-19 diseases. Moreover, we also elaborate on the recommendations for CGT developers to be better prepared for any future pandemic, as well as implications for optimised strategies to ensure that market access of CGTs is not hampered by the COVID-19 pandemic.

Disruption of all activities

Supply chains and manufacturing

The supply chains of CGTs, which were already logistically complicated before the pandemic [4], have had to face new challenges as the disease has rapidly evolved. The first challenge comes from the shortage of supplies of materials for CGTs.

A tendency toward a shortage of material supplies is particularly the case for cell-based therapies, which are manufactured either on an allogeneic or autologous basis. For allogeneic products, cell donors have been less likely to donate because of social distancing restrictions, and the US Food and Drug Administration (FDA) requires a 28-day investigation before donation for donors with a confirmed or suspected COVID-19 infection [5]. For autologous products, cell collection from patients, the first step in the manufacturing process, requires human-to-human contact, including a visit to an apheresis centre and interaction with apheresis technicians [6]. However, many apheresis centres have suspended operations to limit the risk of exposure to clinicians. Furthermore, because of the short shelf-lives of cell therapies (CTs), the manufacturing and supply of autologous CTs often requires that the shipment of fresh cell material to manufacturing sites, and the transportation of manufactured products from manufacturing sites back to administration centres, must be done within tight timeframes [4,7]. Disruptions to travel itineraries put those shipments at risk. For example, the ban on travel from Europe to the USA has caused threats to the shipments of Novartis' Kymriah®, delivery of which is time sensitive [8]. Although Novartis has stated that it has found alternate methods to ship Kymriah®, not all biotechnology companies are financially and technically competent to navigate such hurdles. Approximately one-third of CTs companies have reported delays or discontinuation of manufacturing activities in a virtual roundtable [9].

Regarding manufacturers of gene therapies (GTs), their already constrained manufacturing capacity for viral vectors before the COVID-19 crisis might have become even tighter [10]. This is because many of the raw materials used to manufacture viral vector-based vaccines are the same as those used to manufacture GTs [11]; thus, raw materials have been transferred to develop and manufacture what could be billions of doses of COVID-19 vaccines [12].

Clinical trials

Many non-COVID-19-related clinical studies have been halted to meet the requirements of the COVID-19 response, or to reassign medical personnel to combat the pandemic [13]. It was estimated that at least 322 trials conducted by biopharma companies have suffered up to July 2020. The majority of disrupted trials were Phase II trials (44.8%), but early Phase I (26.1%) and pivotal Phase III trials (21.7%) were also affected [14]. FDA officer, Peter Marks, commented that some Phase III clinical trials for GTs might not proceed optimally as planned [15]. Delays in pivotal studies implies that market approval of CGTs in the near future could be affected.

According to a GlobalData report, although the total number of trials disrupted by COVID-19 since June 2020 has declined slowly, the number of trials with difficulties in patient enrolment continues to increase [16]. The slow enrolment could be more evident for clinical trials of CGTs. This is because CGTs can only be administrated by a few specialised medical centres, sometimes requiring patients to travel long distances to participate [10]. More than half of the CGT companies surveyed by McKinsey reported difficulties in recruiting patients or having to suspend trial enrolment to minimise the risk of contracting COVID-19 [9]. In particular, COVID-19 raises specific operational challenges to clinical trials for CGTs targeting rare diseases, which already struggled to recruit enough patients before the crisis [17]. A recent nationwide survey by the National Organization for Rare Disorders conducted with patients with rare diseases showed that 39% of participants have faced challenges accessing medical care or treatment, and 74% have had a medical appointment cancelled [18]. Travel restrictions, patient concerns about being exposed to COVID-19, and the withdrawal of nonessential services from healthcare centres have been contributing factors.

Delivering therapies to patients

The capacity to prepare and treat patients with CGTs in a hospital setting might be more limited. Treatment sites for CGTs must not only be audited and undergo Foundation for the Accreditation of Cellular Therapy accreditation, but also train personnel on procedures for sample collection, storage, and shipment [10]. This is a time-consuming process for clinical staff, especially at this critical time, when there are shortages of personal protective equipment, and hospital resources (e.g., beds and medical ventilators) are prioritised for patients with COVID-19 [19].

The administration of CGTs has also proved to be problematic. Hospitals and patients are concerned about transmission of COVID-19, with patients themselves unable to visit treatment centres because of travel restrictions. This is particularly true for CGTs because most target patients with more severe diseases and the patients are usually immunocompromised. In addition, some CGTs, such as chimeric antigen receptor (CAR) T-cell therapy, are associated with significant toxicities, such as severe cytokine release syndrome (CRS) and neurotoxicity [19,20]. These potential toxicities usually need to be closely monitored and can require intensive-care units, which have been overloaded with patients with COVID-19 [19,21]. Additionally, the current pandemic has meant that hospitals are in short supply of tocilizumab, a monoclonal antibody for the management of CRS, because severe cases of COVID-19 can cause CRS [6]. This could

lead to a delay in initiating new patients on CAR T-cell therapy. In addition, inpatient administration of CGTs will be subject to diagnostic-related group rules in some countries, and these might not adequately cover all the treatment expenses of providing them on top of the budget allocated for COVID-19 [22]. Indeed, financial constraints of hospitals and patients, aggravated by the COVID-19 crisis, could further limit the access of some patient to costly CGTs [23].

Market access-related activities

For CGT manufacturers, staff shortages have delayed assay development and, hence, submissions of Biologics License Applications (BLAs) to the FDA, which could in turn impact the development and approval timelines allowed by a CGT company [9]. For example, despite success securing European Medicines Agency (EMA) approval of Zynteglo® (betibeglogene autotemcel) in May 2019, Bluebird claimed (in March 2020) that the completion of its BLA submission to the FDA would not be anticipated until mid-2021 [24]. In addition, the BLA submission of LentiGlobin™ (bb1111) for sickle cell disease will be further pushed back to late 2022 because of new chemistry, manufacture, and control (CMC) requirements of the FDA, as well as the optional delays of the partnering contract manufacturing organisation [25].

Regulators were struggling to keep up with their workload, even before the pandemic. As anticipated, they will have to switch a large proportion of their time from CGTs to COVID-related issues (e.g., vaccines and convalescent plasma) [26]. The FDA acknowledges that the pandemic might lead to delays in the expected guidelines for regenerative medicine and advanced therapy developers in the areas of neurodegenerative diseases, genome editing, and CAR T-cell therapies, as well as in their efforts to streamline the development of the guidelines on 'N of 1' therapies for ultra-rare disorders. Moreover, interactions with global regulators trying to create more harmonisation of CGT programs in different countries are also challenging [27]. In addition, CMC inspections can be affected by COVID-19 travel restrictions; for example, the FDA approval of Breyanzi® (lisocabtagene maraleucel) was delayed to February 2021 (planned for November 2020) [28].

HTA committees are also under-resourced, because many members, such as clinicians or allied health professionals, will not be able to participate in assessment meetings [29]. Given the unique biological characteristics and a scarcity of clinical evidence, the assessment of CGTs will be dependent on the opinions of specialised clinical experts [30]. Additionally, HTAs for non-COVID-19-related topics (including CGTs) will be delayed because faster appraisal for COVID-19-related topics is the first priority. For example, the National Institute for Health and Care Excellence has established the RAPID-C19 initiative, which aims to prioritise treatments for COVID-19. This has resulted in pauses of several months of the HTA process for Zynteglo® and Zolgensma® [31,32], despite both being considered life-saving therapies.

The delays in regulatory and HTA responses might also have an unexpected influence on the order of market launch, especially for CGTs that have multiple competitors. For example, Sarepta has missed the goal of initiating Phase III clinical trials for their gene therapy, SRP-9001–102, to treat Duchenne muscular dystrophy by the end of 2020, because of a longer time waiting for FDA feedback than previously [33]. Such delays could enable Pfizer to lead the race to bring their Duchenne muscular dystrophy gene therapy, PF-06939926 (currently in the Phase III trial recruiting stage) to market earlier, thus broadening the approval gap between the two products. The economic damage of loss of opportunity to launch first could be profound for CGTs targeting rare diseases. The combination of small patient size and the 'curative' potential of CGTs might create a 'winner-takes-all' dynamic, which means that once the initial 'prevalent' patients with a particular rare condition are treated, the remaining market sales of followers will be limited to only newly diagnosed 'incident' patients [34].

Progress made during the pandemic

New treatment opportunities

Despite all the disruptions caused by COVID-19, it has made clear the importance of science and innovation. The biopharma industry has a crucial role because it is one of the few sectors that can really make a difference in the research and fight against COVID-19. This is reflected in many companies, Biotech or Big Pharma, that are working to develop a treatment or a vaccine to counter COVID-19 [14]. This pandemic has caused an unprecedented catastrophe for the world's economies, but does appear to be having positive effects on the biopharma industry [35].

GT companies are particularly well positioned to research and manufacture COVID-19 vaccines, as seen with most of the vaccines for SARS-CoV-2 that have been authorised so far or that are in clinical development: these are mostly mRNA- or DNA-based or viral vector vaccines [36]. The CRISPR/Cas system, which evolved naturally in bacteria to defend against invading phage, has been used to develop fast and accurate diagnostic assays for COVID-19 [37]. CRISPR/Cas-based approaches have also shown the potential to be repurposed in mammalian cells to defend against RNA and DNA viruses [38], although validation of their effects on SARS-CoV-2 in animal models and humans is still needed [39].

In addition, CGT developers have contributed to advancing knowledge on how genetic factors and immunopathogenesis could impact COVID-19 severity [40,41]. In particular, it is indicative that hyper-reactive immunity, such as an increased level of interleukin-6, could increase the occurrence of respiratory distress syndrome (ARDS) [42]. As a result, the identification of possible prognostic-related biomarkers will, in turn, stimulate the development of potential treatments [41]. Among them, CTs, such as mesenchymal stem cells, have shown potential for treating ARDS via mediation of immunomodulation and repair of lung tissue damage [43]. Based on our search of the clinicaltrials.gov database [44], there were 88 clinical trials for CTs underway up to 30 November 2020. Most were in Phase I ($N = 30$, 34.09%), Phase I/II ($N = 28$, 31.82%), or Phase II ($N = 26$, 29.55%). Two products, MultiStem, developed by Athersys, initially for the treatment of stroke; and Remestemcel-L, developed by Mesoblast, initially for the treatment of steroid-refractory graft-versus-host disease (SR-aGVHD) are being investigated in Phase

II/III and Phase III studies, respectively. Remestemcel-L was granted conditional approval for SR-aGVHD by Health Canada in 2012, but it has never been marketed because it did not obtain reimbursement [45]. However, Remestemcel-L has shown potential immunomodulatory properties toward COVID-19-related ARDS [46], which has attracted Novartis to enter into an exclusive worldwide license agreement with Mesoblast in November 2020 for co-development and co-commercialisation.

According to the annual report released by Cell and Gene Therapy Catapult in November 2020, the manufacturing space of the CGT industry in the UK increased by 48% in 2020 compared to 2019, and several UK CGT developers are investigating viral vector-based vaccines to combat COVID-19 [47]. For example, Oxford BioMedical, which is a pioneer CGT company with a portfolio of LentiVector®-based gene therapies and CAR T-cell therapies, collaborated with AstraZeneca to secure the conditional approval of their adenovirus COVID-19 vaccine, AZD1222, by EMA early in 2021. A German CGT company, BioNTech, which is committed to developing mRNA products and CAR T-cell therapies for solid tumours, has collaborated with Pfizer to produce the mRNA vaccine, Comirnaty (BNT162b2), marking the approval of the first COVID-19 vaccine by the FDA (on 11 December 2020) and EMA (on 21 December 2020). Moderna, which is an mRNA company that has also engaged in gene-editing therapy and regenerative medicines [48], has collaborated with the National Institute of Allergy and Infectious Diseases, and the Biomedical Advanced Research and Development Authority, to redirect its research efforts toward a COVID-19 vaccine, mRNA-1273, which has been authorised by the FDA (on 18 December 2020) and EMA (on 6 January 2021) [49]. All these examples show not only the underlying potential of CGTs, but also how CGTs companies are responding quickly and shifting their strategies to explore more possibilities and to create more value.

Raising finance

Although start-up Biotech companies have suffered dramatically in the pandemic, large companies with stable business lines do not appear to be experiencing a shortage of capital. Biotech companies developing CGTs have had access to unprecedented levels of capital via venture capital (VC), initial public offering routes, or equity investment, even during the pandemic [27]. As shown in the Alliance for Regenerative Medicine report, during the first half of 2020, the regenerative medicine sector had already raised US$10.7 billion, more than the total capital raised in 2019 and a 120% jump over the first half of 2019 [27]. In terms of COVID-19 from a strictly VC perspective, the financial chaos unleashed by the pandemic might have had less of an impact on the Biotech industry than on other key sectors of the global economy. The likelihood of VC shortage for CGT clinical trials in the near-term could be relatively low, especially for Biotech companies that have a sustainable pipeline [35]. The reasons for this could be that investors in the biotechnology field are usually risk tolerant, used to working with loss-making companies, and managing delays and hurdles is 'business as usual'.

Using the internal database of our research group, which gathered all the partnership agreements (e.g., licensing agreements, manufacturing contracts, and joint ventures) for regenerative medicines (including CGTs) made between January 2014 to June 2020, we determined that the total upfront payment for partner-

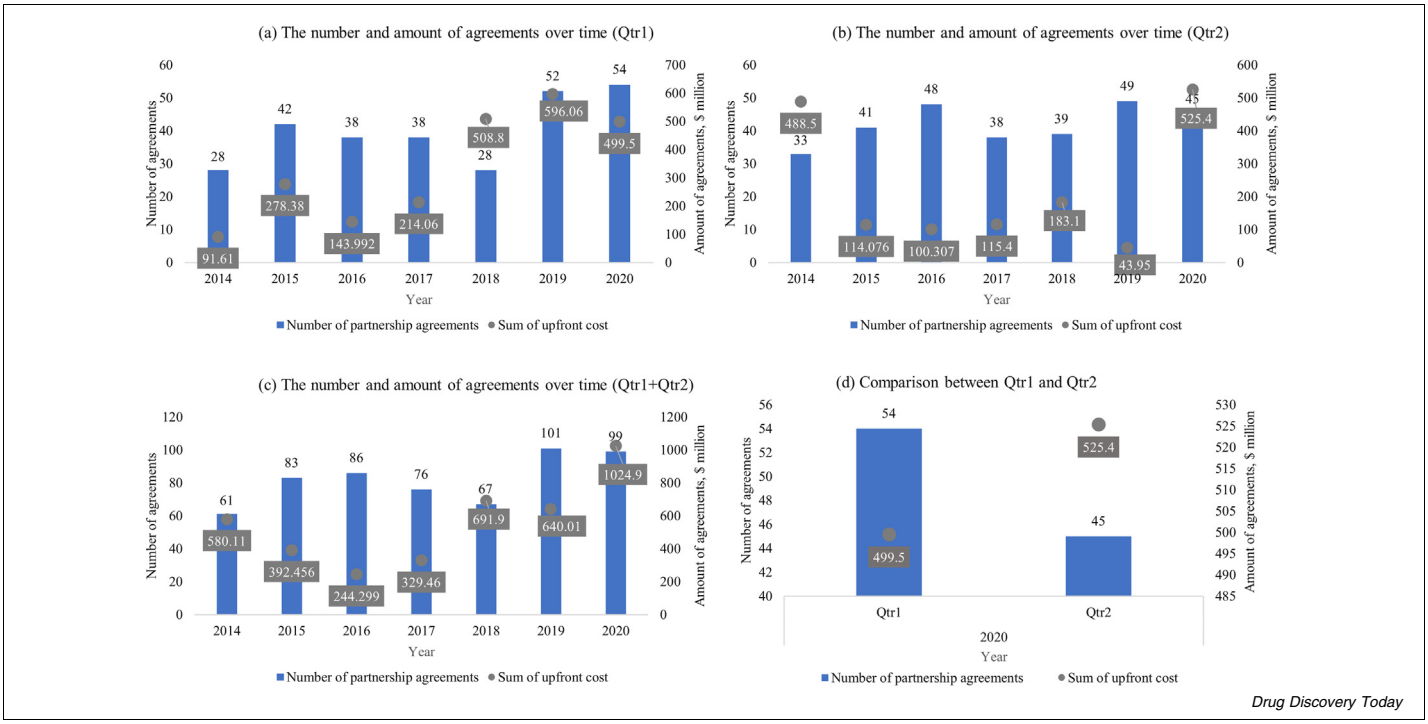

FIGURE 1

Financing raised by partnership agreements for cell and gene therapies (CGTs) during the first half of 2020. The number and amount of agreements over time in **(a)** Quarter 1, **(b)** Quarter 2 and (**c**) Quarter 1+Quarter 2. **(d)** Comparison between Quarter 1 and Quarter 2 of year 2020.

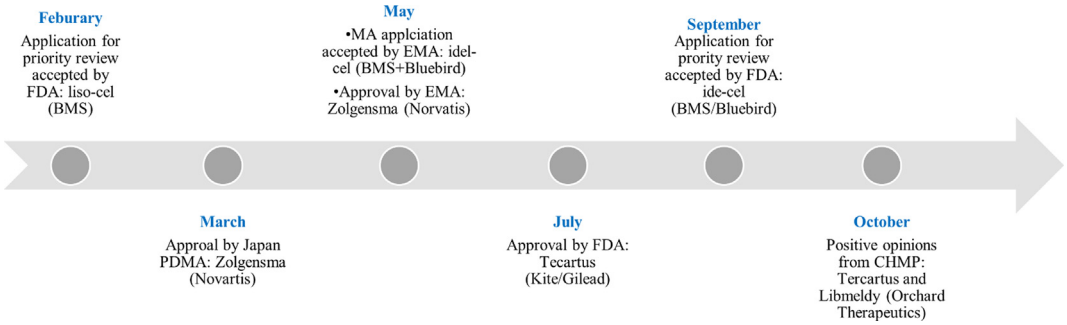

FIGURE 2

Milestones in the regulation of cell and gene therapies (CGTs) in the EU, USA, and Japan during 2020. Abbreviations: BMS, Bristol Meyers Squibb; CHMP, Committee for Medical Products for Human Use; EMA, European Medicines Agency; FDA, US Food and Drug Administration; MA, Marketing Authorisation; PDMA, Pharmaceuticals and Medical Devices Agency.

ship deals involving CGTs has already reached US$1024.90 million by the end of the first half of 2020 (Fig. 1), which considerably surpassed the upfront payment raised for previous years. This was still true during the second quarter of 2020, when the pandemic has rapidly spread across the globe, indicating that the COVID-19 pandemic did not drive investors away from participating in development-related activities of CGTs. Additionally, merger and acquisition agreements related to CGTs made by 'Big Pharma' continued to increase, the notable ones being the acquisition of Allergan by AbbVie for US$63 billion in May 2020; the acquisition of AskBio by Bayer for US$4 billion in October 2020; and the acquisition of Prevail Therapeutics by Lilly for US$1 billion in December 2020. In general, these figures for acquisition appear to be smaller than in 2019, predominantly because of the acquisition of Celgene (by Bristol-Myers Squibb for US$73 billion) and Shire (by Takeda for US$62 billion). This is less surprising because most CGTs are still in a relatively nascent stage of development (e.g., discovery or preclinical) [50] and acquisition bears more risk than partnerships, which appears more obvious at this critical time.

Regulation milestones

Despite all the distractions, it is still good to hear that some CGT developers and regulators continue to manage to advance late-stage CGT candidates to the global market. Tecartus®, a CAR T-cell therapy developed by Kite (a Gilead company) for large B cell lymphomas, was approved by the FDA in July 2020 (Fig. 2). As an FDA officer stated, products with Breakthrough Therapy designation or Regenerative Medicine Advanced Therapy (RMAT) designation remained high priority after COVID-19-related products [51]. As of the end of 2020, 12 CGTs had been granted with RMAT designation by the FDA, including MultiStem for ARDS (Table 1).

From the EMA side, Zolgensma®, a gene therapy developed by AveXis (a Novartis company) for spinal muscular atrophy, was approved in May 2020. Tecartus® and Libmeldy® (developed by Orchard Therapeutics for metachromatic leukodystrophy), received positive recommendations for market authorisation from the Committee for Medicinal Products for Human Use in October 2020 (Fig. 2). As of the end of 2020, nine CGTs had been granted with priority medicines designation (Table 1).

Additionally, it is encouraging to see that regulators have committed to facilitate the scientific review and approval timeline of treatment for COVID-19. The FDA has created a special emergency program, the Coronavirus Treatment Acceleration Program, with the goal of using every available method to bring possible COVID-19 treatments to patients as quickly as possible, while at the same time validating whether they are helpful or harmful. The Emergency Use Authorization (EUA) is able to operate where unapproved medical products or unapproved uses of approved medical products are allowed to be used in an emergency for life-threatening diseases or conditions when there are no available alternatives. As of 25 December 2020, the EUA had granted ten drug and biological products EUA status (including the BNT162b2 and mRNA-1273 vaccines, but excluding the revocation of hydroxychloroquine and chloroquine phosphate) [52]. The EMA has also established a COVID-19 pandemic Task Force to take quick and coordinated regulatory actions on the development, authorisation, and safety monitoring of treatments and vaccines that are intended for the treatment and prevention of COVID-19.

Although there are no CGTs that have been approved to treat COVID-19, companies that are developing CGTs for COVID-19 would benefit from these measures, including more intensive interactions with regulators to obtain scientific advice and to facilitate clinical development. Considering the large number of patients with COVID-19 to be treated and tested in clinical trials, this will provide more insights into the safety and effectiveness of CGTs more quickly. By contrast, albeit an exceptional example, the delay of Zynteglo® in the USA could provide new opportunities for Bluebird to seek approval for a broader patient population, including patients with β^0/β^0 genotypes and paediatric patients [25], rather than restricting to patients older than 12 years old without a β^0/β^0 genotype, as allowed by the EMA. The implication is that COVD-19 could bring unexpected posi-

TABLE 1

CGTs receiving RMAT and PRIME designation in 2020.[a,b]

Product (active ingredient)	Developer(s)	Indication	Date
RMAT			
MultiStem (multipotent adult progenitor cells)	Athersys	ARDS	23/09/2020
CTX001 (autologous CD34$^+$ stem cells with CRISPR-edited *BCL11A*)	CRISPR Therapeutics and Vertex	Severe haemoglobinopathies	11/05/2020
Ilixadencel (activated allogeneic dendritic cells)	Immunicum AB	Metastatic renal cell carcinoma	06/05/2020
MDR-101 (cellular therapy comprising kidney donor-derived CD34$^+$ HSCs and CD3$^+$ T cells)	Medeor Therapeutics	Prevent kidney transplant rejection without chronic use of immunosuppressive drugs	22/09/2020
Kymriah® (tisagenlecleucel)	Novartis	Relapsed or refractory (r/r) follicular lymphoma	22/04/2020
Orca-T (T cell-depleted graft with additional infusion of conventional and regulatory T cells)	Orca Bio	Patients with blood cancers eligible for haematopoietic stem-cell transplantation (HSCT)	15/10/2020
CD30-directed autologous CAR-T cell therapy	Tessa Therapeutics	Relapsed or refractory CD30-positive Hodgkin lymphoma	27/02/2020
AB205 (universal E-CEL® Cell Therapy)	Angiocrine Bioscience	Organ vascular niche injuries for prevention of severe toxicities in patients with lymphoma	11/11/2020
AMDC-USR (autologous muscle-derived cells for urinary sphincter repair)	Cook MyoSite	Women with persistent or recurrent stress urinary incontinence following surgical treatment	17/12/2020
TTAX02 (human umbilical cord product)	TissueTech	Spina bifida *in utero*	16/04/2020
Adenovirus-associated viral vector serotype 5 containing *RPGR*	MeiraGTx	X-linked retinitis pigmentosa resulting from defects in retinitis pigmentosa GTPase regulator	27/02/2020
PRIME			
ADP-A2M4 (transduced CD4$^+$ and CD8$^+$ cells)	Adaptimmune	Treatment of HLA-A*02-positive patients with inoperable or metastatic synovial sarcoma	23/07/2020
ALVR-105 (allogeneic multi-virus-specific T lymphocytes)	AlloVir	Serious infections with BK virus, cytomegalovirus, human herpes virus 6, Epstein–Barr virus, and/or adenovirus in allogeneic HSCT recipients	30/01/2020
AT-GTX-501 (adeno-associated viral vector, serotype 9, containing human CLN6)	Amicus Therapeutics	Paediatric patients with variant late infantile neuronal ceroid lipofuscinosis 6 (vlincl6)	17/09/2020
BB1111 (autologous CD34$^+$ cell-enriched stem cells transduced with BB305 lentiviral vector encoding βA-T87Q-globin gene)	Bluebird bio	Sickle cell disease	17/09/2020
CD30-directed genetically modified autologous T cells (CD30.CAR-T)		Classical Hodgkin lymphoma	17/09/2020
CTX001 (autologous CD34 + haematopoietic stem cells with CRISPR-edited erythroid enhancer region of *BCL11A*)	CRISPR Therapeutics and Vertex	Sickle cell disease	17/09/2020
OTL-203 (autologous CD34 + haematopoietic stem and progenitor cells with lentiviral vector encoding alpha-L-iduronidase)	Orchard Therapeutics	Mucopolysaccharidosis type I	17/09/2020
ECT-001-CB (UM171-expanded cord blood transplant))	ExCellThera	Urgent allogeneic haematopoietic stem cell transplantations	10/12/2020

[a] Abbreviation: PRIME, priority medicine.
[b] Data as of the end of 2020 for RMAT designation; 12 RMAT designation granted in total, only ten of which publicly announced are listed. Data as of the end of 2020 for PRIME designation.

tive impacts to CGT manufacturers by offering breathing space for them to rethink their development plan and to be better prepared for further disruptions.

Recommendations to manufacturers

Increase resilience in manufacturing and supply chains

Manufacturing remains a rate-limiting factor in the production of CGTs. Finding ways to address bottlenecks during the current manufacturing processes is crucial to ensure business continuity and improve resilience for coping with future disruption. Although more viral vector-manufacturing capacity is the long-term answer, CGT companies might consider strategic partnerships with key suppliers of crucial raw materials and viral vectors, or identify and validate two to three potential suppliers early during the development process, rather than relying on just one [9]. This strategy might have an impact on the cost of development because the equivalence between vectors from different sources should be proven. Back-up vector producers will require substantial investments to secure their ability to produce the requested vector on the spot.

Other means of optimising the CGT supply chain might include an expansion of donor bases [12], and the use of pre-emptive, cryopreservation of manufactured cell-based products before cell infusion to ensure timely administration after completion of lymphodepletion conditioning chemotherapy [53]. For example, Kymriah® might be a preferred choice at this time because leukapheresis is cryopreserved before shipment, although it might not apply to another CAR T-cell therapy pro-

duct, Yescarta®, which will require fresh leukapheresis to be transported across the border [53]. Furthermore, the distance between manufacturing facilities might be reduced as companies realise the importance of easy patient access to them. This could result in an increased clustering of manufacturing facilities [54]. Again, the additional cost needed for decentralising manufacturing facilities will be neutralised by the increased volume of production and use.

A more resilient manufacturing and delivery model might require a completely different approach, possibly bringing the manufacturing and delivery of therapies to a single site: the point of care (POcare) [55]. For example, Orgenesis has established partnerships with the University of California to utilise an automated, closed, POCare platform, which will enable each hospital to design and manage localised clean rooms for CGT manufacturing and administration independently. As a result, POCare manufacturing will not only reduce cost and production time, but should also have a wider uptake [56].

Business continuation with supportive measurements

Prepare for digitalisation

Unlike traditional biopharma, CGT companies must be involved in both upstream and downstream processing activities, starting from raw material collection, all the way through to delivery to the patient. This process can be resource intensive and requires specialised knowledge and technological support. Digitalisation is expected to reduce the time needed to translate CGTs from laboratory tests to commercial use [26]. For example, digitalisation could be used to promote virtual audits if risk-based approaches are taken, and the audit partner would have the ability to send documentation in an efficient way [26]. Not surprisingly, companies that are beginning to scale up manufacturing as their businesses grow might also reconsider the criteria for selecting manufacturing partners. Reliability and preparedness for digitalisation might be valued more highly during the current crisis when regulatory site inspections are restricted [9].

Telemedicine and decentralised clinical trials

As mentioned earlier, the pandemic has caused severe disruption of clinical trials because patients are unable to visit clinics to participate, and researchers are unable to monitor and make postadministration outcome assessments. This points to the future, where telemedicine could be applied in the outcome assessment of decentralised clinical trials, which are studies that could be designed to reduce dependency on specialised research centres and expand the reach to patients' workplaces or homes [57]. Clearly, if there are validated outcome measures that could be captured reliably in remote locations via telemedicine, the development of CGTs will ultimately be facilitated [58] by means of promoting patient recruitment and improving adherence to follow-up schedules. This could be particularly relevant for clinical trials of CGTs, because that postlaunch evidence collection is mandatory for CGTs (e.g., 15 years of monitoring is required by the FDA), whereas patients who are very sick or with a disability will no longer need to travel long distances to specialised medical centres for follow-ups [51]. Given that administration of CGTs will required invasive operations and tight coordination among multiple healthcare professionals, the initial participation of clinical trials will still take place in hospital settings [59]. Although feasible remote approaches might increase within-subject variability in the collection of patient-reported outcomes (PROs), thus the preferred collection method (e.g., email, telephone, and internet) should be determined based on the specifics of the clinical questions to be answered and the PRO instruments used [13].

Stay close with other stakeholders

Engagement with patients and healthcare providers

Patient engagement has had an important role in each step of CGT development, from capturing manufacturing material, clinical trial participation, collection of PRO evidence, involvement in regulatory activities, and conduction of postlaunch studies to advocacy for market access [60]. Nevertheless, limited knowledge or even misunderstanding of the potential benefits and risks of CGTs can undermine the patient willingness to participate in clinical trials [61]. Understandably, patients currently might be more concerned about the risks of infection and toxicity related to CGTs than ever before [62]. Therefore, patient engagement during this crucial time is imperative to improve trial enrolment and to ensure that patients adhere to the proposed trials and are fully informed about any protocol modifications [63]. Additionally, social distancing and lockdown might affect patient mental health and quality of life, thus influencing PRO responses in multiple ways. Sufficient communication with patients to understand the possible confounding factors (e.g., regional policies, epidemiology of the pandemic, patient symptoms, and COVID-19 infection status) will be meaningful to better interpret the PRO response and to assess the potential for bias [64]. This will also help to reach more reasonable explanations for patient drop-out, thus supporting the selection of suitable statistical approaches (e.g., last observation carried forward) to deal with missing PRO data [64].

It is probable that engagement with healthcare providers is of equal importance to patient engagement because patients tend to trust and rely on them to make suitable medical decisions related to CGTs treatment [61] (Table 2). Delaying some life-saving CGTs treatments because of COVID-19 is not a realistic option owing to disease severity and rapid progression [19,53]. Therefore, interactions with healthcare providers (including physicians, nurses, pharmacists, radiologists, and others) are imperative to ensure that CGT treatments are delivered to patients who are in urgent need (e.g., who have more aggressive medical conditions that lack alternative treatments) in accordance with strict operational standards [65]. Meanwhile, supportive measurements are in place to provide sufficient protection during the material sourcing and administration process [19]. Again, with the application of telemedicine, efforts must be devoted to ensuring that both patients and healthcare providers are comfortable and familiar with the methods of remote assessment [58].

Collaboration with other researchers or developers

CGTs hold promises for rare diseases that are currently lacking effective treatments, whereas the development of orphan drugs is typically a lengthy process with many failed attempts. Apart from insufficient knowledge of disease characteristics and the

TABLE 2

Collaborative efforts among all stakeholders to secure market access of CGTs during the COVID-19 pandemic.

Stakeholders	Collaborative activities
Other researchers or developers	Improve manufacturing resilience to COVID-19 disruptions by engaging with multiple reliable collaborators. Digitalisation capacity could serve as a criterion for deciding who to be partnered with Research networks among multiple pharmaceutical companies to streamline sharing knowledge and resources of CGTs for rare diseases Enhance clinical data sharing for better informing design of trials
Patients	Enhance patient engagement throughout development process to understand natural history of the disease; to support patient recruitment; to collect PRO in clinical trials and postmarket studies; and contributed to regulatory and HTA-related activities Interactions to ensure that patients are sufficiently informed about the potential benefits and risks of CGT treatment during pandemic, and secure patient compliance with clinical trial protocol Education for use of telemedicine tools for PRO evidence collection in follow-up studies during COVID19
Healthcare providers	Collaboration with healthcare providers to set up sufficient infrastructures for manufacturing and administration of CGTs to ensure that delivery of CGTs is not delayed and operation standards are followed despite COVID-19 disruptions Collaboration with healthcare providers to educate on use of digitalisation and telemedicine, to reduce burdens on management and monitoring of CGTs during COVID-19, and to increase clinical adoption
Regulators	Early dialogue between regulators and CGTs developers to communicate potential protocol deviations for manufacturing, quality control, clinical trials, and postmarket studies because of COVID-19 Approach regulators to discuss feasibility of remote inspections with digitalisation techniques to cope with travel restrictions
HTA bodies and payers	Early dialogue between HTA bodies and CGT developers to communicate potential protocol deviations for clinical studies because of COVID-19 (i.e., alternative statistical analysis for missing data) and to understand adjustments to evidence requirements Approach payers to discuss feasibility and possibility of alternative payment mechanisms (e.g., outcome-based payment) to ensure that economic recession caused by COVID-19 will not significantly delay patient access to life-saving CGTs

small number of patients with rare diseases, other contributing factors include dedicated researchers being geographically scattered, [66] and large amounts of preclinical and clinical data not being publicly accessible [67].

Therefore, there is an urgent call to enhance collaborations across different CGT developers for rare diseases (Table 2); this is particularly the case during the current pandemic, with resource shortages and restrictions on research activities being notable issues. Such collaborations could provide benefits in terms of promoting data sharing and improving efficiency by reducing duplicative work [66]. From a manufacturer's perspective, this could happen in two ways: (i) proactively engage with the global research network for rare diseases and CGTs to enhance the sharing of medical knowledge (e.g., disease or technology related) [68], such as the International Rare Diseases Research Consortium and the International Society for Cell and Gene Therapy; and (ii) empower clinical data sharing (including negative study results) to optimise the design and quality of clinical trials, as seen in the heterogeneous strategies adopted by pharmaceutical giants [17,67]. Notably, this must be achieved alongside adequate protection for patient privacy and commercial confidentiality, in addition to appropriate regulatory guidelines in place to ensure that shared data are not misused or misinterpreted [67].

Interactions with regulators

Considering that challenges for clinical trials and manufacturing are aggravated by COVID-19, there is a possibility that noncompliance with clinical trial protocols and Good Manufacturing Practice of CGTs could be higher than during prepandemic times. However, for CGTs, deviation from trial protocols and invalidation of manufacturing-related analytic methods were observed to be common reasons for objections from regulators [69]. Another common reason for objections to CGTs is the clinical data package, covering issues of study design, lack of randomisation, variability in the different analyses of clinical outcomes, and choice of comparators for historical control [70,71]. As expected, more regulator objections will be associated with a longer overall regulatory procedure duration [70].

Therefore, for CGT companies, excellent connections with regulators are important to discuss and mitigate any regulatory issues [3], such as data gaps and protocol deviations (e.g., frequency of follow-up), which might have arisen during the COVID-19 crisis. As suggested in the newly released FDA guidelines on the Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency [72], consulting the FDA is strongly advised for complex investigational products (e.g., CT and GT products), whereby potentially altered storage and handling conditions could adversely affect product stability. In addition, good relationships forged now might help CGT companies to benefit from the increased openness that regulators have demonstrated in their response to COVID-19, which could well extend to the future regulation of CGTs. For example, more flexibility might be allowed for deviations from published statistical analysis plans and acceptance of alternative statistical analyses [29] (Table 2).

Collaborations with HTA bodies and payers

HTAs for clinical evidence

The openness of regulators might not always represent the same favourable attitudes of HTA agencies. For example, in May 2020, the Institute for Quality and Efficiency in Health Care (IQWIG),

the HTA agency in Germany, wrote to the EMA calling for full transparency of the methods used, and the results obtained from clinical trials for COVID-19 to ensure public confidence and trust [73].

Beyond COVID-19-related products, this implies that the complexity involved in making a robust HTA for CGTs will be further amplified by the pandemic. This is because clinical trials for CGTs typically feature small patient numbers [34], whereby the problems of missing data or censored data become even more pronounced because of COVID-19. The inherent uncertainties in the single-arm trials of CGTs will become more evident because alternative analytic methods are used to adjust the missing data. Moreover, it will be more difficult to conduct comparative studies for CGTs targeting life-threatening rare diseases, which mostly lack an alternative treatment available to serve as active comparator [30], whereas the willingness of patients to participate in placebo-controlled trials will be lower at this crucial time because of the unpredictability of trial group assignment and an increased risk to virus exposure [17]. An indirect comparison will also be questioned regarding whether it is appropriate to combine the clinical trials conducted during the pandemic with the clinical trials conducted before the pandemic [13]. Moreover, patients treated with CGTs, who usually have severe conditions, will be at a higher risk of mortality and complications if they become infected with COVID-19 [74], thus an accurate estimation of overall survival will be compromised. Another potential bias posed by the COVID-19 pandemic includes incomplete follow-ups (possibly not at random) that might invalidate the planned analyses. In addition, potential heterogeneity in the included patients might increase, especially for multicentre trials, because the prevalence/incidence data vary across regions, thus widening the confidence interval of outcome estimates [75]. All these factors will contribute to an increased uncertainty in the magnitude of treatment benefits of CGTs, and the appropriateness of clinical inputs for an extrapolation model [30], making a robust HTA on clinical evidence of CGTs challenging.

Cost-effectiveness and value assessment

On the other side, the impact of adaptive study designs and alternative analytical approaches in clinical trials on the HTA acceptance of cost-effectiveness results of CGTs is inconclusive, in addition to uncertainty in whether the threshold of willingness-to-pay [74] will alter because of the economic recession in most countries worldwide.

Moreover, there is another question related to the cost-effectiveness analysis, in terms of the perspective from which the value and costs will be measured. CGTs could generate indirect, nonhealth benefits in terms of returning patients to their work and school, as well as cost savings from improved productivity [76]. Such benefits are relevant not only to patients and their family, but also to society. Additionally, CGTs for serious diseases, via one-off or limited times of administration, might reduce the amount of healthcare that many patients need for regular treatments (e.g., factor replacement for haemophilia) during the COVID-19 crisis [77], which is another economic advantage provided by CGTs that should be included. A robust economic analysis of CGTs will require value assessment and cost calculations to take societal benefits, outside the healthcare sector, into consideration [30] to avoid underinvestment in future innovation and to ensure the availability of life-saving CGTs that are in urgent need [76].

Beyond health-related issues, these broader societal, economic impacts of COVID-19 have become one of the major focuses of government attention, whereas these factors appear to be overlooked and arbitrarily considered in the assessment of CGTs. This implies that communication between CGT developers and decision-makers is crucial to develop optimal frameworks to standardise the methods for measuring indirect costs and values. Specifically, more clarification is needed in terms of the appropriate cost and value elements to include, as well as the appropriate approach to estimate and quantify them [78]. Although this problem existed long before the pandemic, new issues have arisen because COVID-19 might further increase the temporary and permanent productivity loss from the perspective of both patients and society as a whole [79]. Therefore, the additional value brought about by CGTs because of increased productivity will possibly be appreciated more in the future.

Pricing

The high price of CGTs was already a controversial issue that was under extensive scrutiny before the COVID-19 crisis [23]. Manufacturers claimed the high price of CGTs was to recoup the research and development (R&D) and manufacturing costs, and this raised intensive debate given the nondisclosure of the full R&D cost by manufacturers, combined with more recent estimates suggesting a lower R&D cost for innovative drugs compared with past figures [80]. Another overlooked factor is that the development of CGTs for rare diseases is often partially funded by the public sector; thus, a lower price deducting this already-paid cost should be more justified and reasonable [81]. Most importantly, there are continuous debates regarding whether the long-term clinical benefits of GTs justify the high price tag [56]. Therefore, to ensure that patients continue to have sufficient access to these therapies, CGT manufacturers will be urged to find solutions to optimise the cost of CGTs to the greatest extent possible.

Manufacturers of CGTs will also need to discuss more carefully with payers how to price these high-cost therapies [82]. For the time being, most CGTs companies do not foresee a major shift in their portfolio strategies, but there is little doubt that some might need to reassess the value of their individual assets and reprioritise R&D efforts by incorporating economic considerations (e.g., logistics or development resilience), earlier on in decision processes [83]. In addition, now, more than ever before, CGT companies will need to demonstrate that the costs of their treatments are offset by the potential values measured in patient benefits and long-term downstream cost savings [23]. In other words, value-based prices will be the more optimal solution, whereby the price of CGTs will be directly linked to the additional values brought by introducing them. Again, more clarification of the methods used for the assessment and quantification of additional values is required for its implementation.

Reimbursement and payment

Nevertheless, despite being cost-effective, value-based prices might still be too high to be affordable [84]. It was estimated that the 5-year total cost impact of GTs for rare blood disorders (including haemophilia A, haemophilia B, beta-thalassemia major, and sickle cell anaemia), will be US$10 970 million (assuming a price of US$1 million and 30% market penetration) to US $31 860 million (assuming a price of US$2 million and 40% market penetration for *ex vivo* therapies and *in vivo* therapies) [85]. It appears overoptimistic to expect that all these CGTs will be reimbursed at such prices without restrictions, especially because healthcare systems are already under pressure and there might be more budget constraints with the pandemic and launch of COVID-19 vaccines. According to the World Bank Global Economic Prospects released in June 2020, the global economy was estimated to shrink by 5.2% in 2020, representing the deepest recession since World War II [86]. As an indirect result of COVID-19-related budgetary pressure, more restrictions on the reimbursement and market access for costly drugs will be expected [77]. This could include lower pricing or increased taxes, age restrictions to access, delayed or denied coverage, and/or increasing administrative barriers to qualifying for reimbursement [87].

For example, France and Germany have historically expressed more openness and a higher acceptance toward innovative products that hold potential for severe diseases with high unfulfilled medical needs, in contrast to the UK, where the cost-effectiveness outcome constitutes the key criterion for decision-making [88]. In Germany, in particular, the additional benefits of orphan drugs are considered to be proven and automatically reimbursed by law following EMA approval [88]. However, for the first time, in July 2020, during the review of Zolgensma®, the Gemeinsame Bundesausschuss (G-BA) explicitly specified the rules for postlaunch evidence collection for orphan drugs approved, with considerable evidence of uncertainties. Once determined that additional data collection is necessary, the IQWIG, on behalf of the G-BA, will draft concepts, including the detailed requirements of: type, duration, scope, methods of data collection, and the patient-relevant endpoints to be considered as outcomes. In addition, the G-BA stated that, at least every 18 months, they will evaluate whether data collection is being carried out or can no longer be carried out, whether it will provide sufficient evidence for a renewed benefit assessment, or whether there is a need for adjustments to the provisions of the decision [89]. Such initiatives indicate that a more prudent attitude toward reimbursing CGTs and stricter requirements on fulfilling postmarketing scientific obligations will be expected in the future. In France, the HTA decisions of Haute Autorité de Santé (HAS) for Zynteglo® (released on 26 March 2020) and Zolgensma® (released on 18 December 2020) are informative examples of how payers will apply more restrictions on reimbursement: Zynteglo® was only reimbursed for transfusion-dependent beta-thalassemia in patients aged over 12 years but less than 35-years old, rather than the EMA label including all patients older than 12 years old [90], Zolgemsma® was only reimbursed for spinal muscular atrophy (SMA) type I (i.e., the most severe type of SMA), rather than the EMA label including SMA type I, and a certain number of patients with SMA type II and type III (i.e., less severe types of SMA) [91]. This is a predictable and unavoidable trend that would have happened sooner or later: COVID-19 simply acted as an instigator to make it happen now.

Furthermore, in response to financial constraints, payers will become more risk averse, and will rely more heavily on innovative payment mechanisms, such as outcome-based payments and instalment payments (used as stand-alone or in combination with outcome-based agreements) [92], to connect the price with the potential value delivered [93]. The existing reimbursement system is not designed for innovative payment models, but sometimes there are administrative and structural barriers to accommodate these new models [93]. For example, to remove the legislative barriers in the implementation of value-based payments, the Centers for Medicare and Medicaid Services proposed a change of the 'Best Price' rule in June 2020. This highlights a possible shift that payers begin to recognise the importance of implementing innovative payment mechanisms to facilitate market access of promising products without threatening financial sustainability [77]. For example, Zolgensma® (priced at US $2.1 million) and Zynteglo® (priced at US$1.78 million), as the two most expensive drugs in the world, have both engaged in an outcome-based instalment payment spread over 5 years, which results in a per-year cost of US$425 000 and US$383 000 for Zolgensma® and Zynteglo®, respectively [94]. Successful implementation of these innovative models will call for collaborative efforts between payers and manufacturers of CGTs to ensure that relevant and realistic clinical milestones are defined, and payment terms are mutually beneficial (Table 2).

Given the loss of follow-up or protocol deviation during the pandemic, postmarket evidence collection required for the validation of long-term outcome of CGTs could be affected. More conversations with HTA bodies and payers are needed to ensure that rationales for modifications are fully communicated, and requirements for robust evidence collection for reassessment are adequately satisfied. Furthermore, the patient registry for CGTs might be more susceptible to potential bias toward less severely ill patients because of the COVID-19 pandemic; this calls for measurements to ensure that the patient registry contains a well-stratified patient population, which could be achieved through ownership of the patient registry by government agencies, and the governance of the registry overseen by an independent third party via reliable logistic supports [95]. More than ever before, the importance of coordination across decision-makers (i.e., regulators and payers) and collaboration across countries should be highlighted to improve the consistency and efficiency of postlaunch real-world evidence collection [95]. This is of particular significance for CGTs, which are typically indicated for rare diseases with small patient populations [96] and for which administration is concentrated in a limited number of specialised medical centres [95].

Concluding remarks

The COVID-19 pandemic has caused significant disruption to the research, manufacturing, clinical development, and market launch of CGTs for non-COVID-19-related diseases. A shortage of supplies of materials for manufacturing, difficulties in clinical trials (e.g.,

patient recruitment, conduct of placebo-controlled trials, and follow-up), and a delay in regulatory dossier preparation are all contributing factors. This has emphasised the importance of addressing the challenges in the manufacturing and supply chain of CGTs to improve resilience during the crisis. Digitalisation will improve the quality and accuracy of manufacturing and regulatory documents through increasing the traceability of the whole journey of CGTs. Telemedicine will be a powerful technique to mitigate the loss of follow-ups in clinical trials, especially for CGTs with indications for rare, life-threatening disorders.

Nevertheless, compared with other key global sectors, it is encouraging to see that some biopharma companies are shifting their focus and leveraging their decades of innovation experience to explore therapeutic options for the COVID-19 pandemic. Developers of COVID-19-targeted CGTs will benefit from more interactions with regulators to obtain timely scientific advice on their clinical programs, which will in turn support them to gain insights into how to proceed with their non-COVID-19 programs in the future. Developers of non-COVID-19-related CGTs are also advised to keep close relationships with regulators to report the protocol deviation of clinical trials, and to better understand the possible adaptations in evidence requirements. The disruption of clinical trials will further prejudice the quality of clinical evidence for CGTs, making it even more challenging to achieve a reliable HTA on the treatment benefits and economic impacts of CGTs. A foreseeable economic recession because of the pandemic will make payers become more risk adverse and financially sensible. The high price of CGTs will urge manufacturers to enhance communications and negotiations with payers to reach mutually beneficial solutions to minimise the delay in the market access of CGTs. Innovative payment mechanisms will be increasingly applied to facilitate patient availability of CGTs and to maintain financial sustainability in the meantime. There are still methodological (e.g., outcome and value assessment), administrative (e.g., data infrastructure), structural (e.g., reimbursement system), and legislative (e.g., transfer of instalment payments obligations to following payers) barriers that must be removed before the broad adoption of innovative payment models become a reality.

Most importantly, collaborations between all relevant stakeholders involved in the CGTs must be emphasised, and this will be the only solution to ensure that such an unprecedented crisis will not jeopardise timely market access of CGTs to patients who are desperately waiting for life-saving treatments.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

We acknowledge Marcus Bashford from ApotheCom for providing medical writing support.

References

[1] K. Leung, J.T. Wu, D. Liu, G.M. Leung, First-wave COVID-19 transmissibility and severity in China outside Hubei after control measures, and second-wave scenario planning: a modelling impact assessment, Lancet 395 (2020) 1382–1393.
[2] WHO. Coronavirus disease (COVID-19) pandemic. Geneva; WHO, 2020.
[3] T. Qiu, E. Hanna, M. Dabbous, B. Borislav, M. Toumi, Regenerative medicine regulatory policies: a systematic review and international comparison, Health Policy 124 (2020) 701–713.
[4] B. Calmels, B. Mfarrej, C. Chabannon, From clinical proof-of-concept to commercialization of CAR T cells, Drug Discov Today 23 (2018) 758–762.
[5] FDA. Rare disease therapy development and access remain top FDA priorities during COVID-19. www.fda.gov/news-events/fda-voices/rare-disease-therapy-development-and-access-remain-top-fda-priorities-during-covid-19. Published June 11, 2020. Accessed April 13, 2021
[6] I. Ortiz de Landazuri, N. Egri, G. Muñoz-Sánchez, V. Ortiz-Maldonado, V. Bolaño, C. Guijarro, et al., Manufacturing and management of CAR T-cell therapy in 'COVID–19's time': central versus point of care proposals, Front Immunol 11 (2020) 573179.
[7] M. Abou-El-Enein, A. Elsanhoury, P. Reinke, Overcoming challenges facing advanced therapies in the EU market, Cell Stem Cell 19 (2016) 293–297.
[8] Fiercepharma. Novartis sidesteps Europe travel ban to provide CAR-T drug Kymriah to patients. www.fiercepharma.com/manufacturing/novartis-sidesteps-europe-travel-ban-to-provide-car-t-drug-kymriah-to-patients. Published March 13, 2020. Accessed April 13, 2021
[9] McKinsey & Company. COVID-1and cell and gene therapy: How to keep innovation on track. www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/covid-19-and-cell-and-gene-therapy-how-to-keep-innovation-on-track. Published August 18, 2020. Accessed April 13, 2021
[10] K. Elverum, M. Whitman, Delivering cellular and gene therapies to patients: solutions for realizing the potential of the next generation of medicine, Gene Ther 27 (2019) 537–544.
[11] Labiotech.eu. Covid-19 forces gene therapy companies to shift strategy. www.labiotech.eu/gene-cell-therapy/covid-19-gene-therapy-shift/, Published July 29, 2020. Accessed April 13, 2021
[12] cell&gene. How COVID-19 is changing the production of cell therapies. www.cellandgene.com/doc/how-covid-is-changing-the-production-of-cell-therapies-0001, Published April 17, 2020. Accessed April 13, 2021
[13] M.A. Psotka, W.T. Abraham, M. Fiuzat, G. Filippatos, J. Lindenfeld, T. Ahmad, et al., Conduct of clinical trials in the era of COVID-19: JACC scientific expert panel, J Am Coll Cardiol 76 (2020) 2368–2378.
[14] S. Kili, Clinical trials in the era of Covid-19: successes, failures ongoing challenges, Cell Gene Ther Insights 6 (2020) 775–782.
[15] Healio. COVID-19, manufacturing challenges limit cell and gene therapy progress, FDA official says. www.healio.com/news/hematology-oncology/20201028/covid19-manufacturing-challenges-limit-cell-and-gene-therapy-progress-fda-official-says. Published October 29, 2020. Accessed April 13, 2021
[16] GlobalData; COVID-19 clinical trial disruption declines but trials continue to suffer from slow recruitment. www.globaldata.com/covid-19-clinical-trial-disruption-declines-trials-continue-suffer-slow-recruitment/. Published October 12, 2020. Accessed April 13, 2021
[17] W. White, A rare disease patient/caregiver perspective on fair pricing and access to gene–based therapies, Gene Ther 27 (2019) 474–481.
[18] FDA. FDA takes additional action in fight against COVID-19 by issuing emergency use authorization for second COVID-19 vaccine. www.fda.gov/news-events/press-announcements/fda-takes-additional-action-fight-against-covid-19-issuing-emergency-use-authorization-second-covid. Published December 18, 2020. Accessed April 13, 2021
[19] V. Bachanova, M.R. Bishop, P. Dahi, B. Dholaria, S.A. Grupp, B. Hayes-Lattin, et al., Chimeric antigen receptor T cell therapy during the COVID-19 pandemic, Biol Blood Marrow Transplant 26 (2020) 1239–1246.
[20] N. Frey, D. Porter, Cytokine release syndrome with chimeric antigen receptor T cell therapy, Biol Blood Marrow Transplant 25 (2019) e123–e127.
[21] Deloitte. Delivering scientific innovation requires operating model innovation, www2.deloitte.com/us/en/insights/industry/life-sciences/operating-models-for-gene-cell-therapy-manufacturing-process.html. Published April 17, 2020, Accessed April 13, 2021
[22] M.D. Whittington, R.B. McQueen, J.D. Campbell, Valuing chimeric antigen receptor T-cell therapy: current evidence, uncertainties, and payment implications, J Clin Oncol 38 (2020) 359–366.

[23] D.R. Carr, S.E. Bradshaw, Gene therapies: the challenge of super-high-cost treatments and how to pay for them, Regen Med 11 (2016) 381–393.
[24] US Securities and Exchange Commission, bluebird bio provides assessment of impact of COVID-19, update on business operations and clinical program development, www.sec.gov/Archives/edgar/data/1293971/000129397120000013/exhibit99120200326.htm, Published March 26, 2020. Accessed April 13, 2021
[25] Bluebird bio. bluebird bio reports third quarter 2020 financial results and highlights operational progress. http://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-reports-third-quarter-2020-financial-results-and. Published November 4, 2020. Accessed April 13, 2021
[26] Regulatory Affairs Professionals Society (RAPS). FDA officials, experts discuss impact of COVID-19 on cell and gene therapies. www.raps.org/news-and-articles/news-articles/2020/10/fda-officials-experts-discuss-impact-of-covid-19-o. Published October 15, 2020. Accessed April 13, 2021
[27] Alliance for Regenerative Medicine (ARM). Advancing innovation during COVID-19-ARM Global Regenerative Medicine Sector Report: H1 2020. https://alliancerm.org/sector-report/h1-2020-report-pdf/ Accessed April 13, 2021
[28] Bristol Myers Squibb. Bristol Myers Squibb Provides Regulatory Update on Lisocabtagene Maraleucel (liso-cel). https://news.bms.com/news/details/2020/Bristol-Myers-Squibb-Provides-Regulatory-Update-on-Lisocabtagene-Maraleucel-liso-cel/default.aspx. Published November 16, 2020. Accessed April 13, 2021
[29] P.K. Lorgelly, A. Adler, Impact of a global pandemic on health technology assessment, Appl Health Econ Health Policy 18 (2020) 339–343.
[30] S. Aballéa, S. Aballéa, K. Thokagevistk, R. Velikanova, S. Simoens, L. Annemans, F. Antonanzas, et al., Health economic evaluation of gene replacement therapies: methodological issues and recommendations, J Mark Access Health Policy 8 (2020) 1822666.
[31] National Institute for Health and Care Excellence. Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia. www.nice.org.uk/guidance/indevelopment/gid-ta10334. Accessed April 13, 2021
[32] National Institute for Health and Care Excellence. Onasemnogene abeparvovec for treating spinal muscular atrophy type 1. www.nice.org.uk/guidance/indevelopment/gid-hst10026. Accessed April 13, 2021
[33] Fiercepharma. Sarepta cites 'overburdened' FDA as factor in DMD gene therapy delay. www.fiercebiotech.com/biotech/sarepta-cites-overburdened-fda-as-factor-dmd-gene-therapy-delay. September 11, 2020. Accessed April 13, 2021
[34] T. Qiu, Y. Wang, M. Dabbous, E. Hanna, R. Han, S. Liang, et al., Current state of developing advanced therapies for rare diseases in the European Union, Expert Opin Orphan Drugs 8 (2020) 417–429.
[35] Epidermolysis Bullosa News. COVID-19 delaying rare disease and gene therapy trials, pharma execs say. https://epidermolysisbullosanews.com/2020/05/29/covid-19-delaying-rare-disease-gene-therapy-trials-pharma-execs-say/. Published May 29, 2020. Accessed April 13, 2021
[36] L.H. Vandenberghe, COVID-19: gene transfer to the rescue?, Hum Gene Ther 31 (2020) 605–607
[37] J.P. Broughton, X. Deng, G. Yu, C.L. Fasching, J. Singh, J. Streithorst, et al., CRISPR-Cas12-based detection of SARS-CoV-2, Nat Biotechnol 38 (2020) 870–874.
[38] R. Ramezankhani, R. Solhi, A. Memarnejadian, F. Nami, S.M.R. Hashemian, T. Tricot, et al., Therapeutic modalities and novel approaches in regenerative medicine for COVID-19, Int J Antimicrob Agents 56 (2020) 106208.
[39] P. Kumar, Y.S. Malik, B. Ganesh, S. Rahangdale, S. Saurabh, S. Natesan, et al., CRISPR-Cas system: an approach with potentials for COVID-19 diagnosis and therapeutics, Front Cell Infect Microbiol 10 (2020) 576875.
[40] S. Ghafouri-Fard, R. Noroozi, R. Vafaee, W. Branicki, E. Pospiech, K. Pyrc, et al., Effects of host genetic variations on response to, susceptibility and severity of respiratory infections, Biomedicine Pharmacother 128 (2020) 110296.
[41] M. Anft, K. Paniskaki, A. Blazquez-Navarro, A. Doevelaar, F.S. Seibert, B. Hölzer, et al., COVID-19-induced ARDS is associated with decreased frequency of activated memory/effector T cells expressing CD11a+, Mol Ther 28 (2020) 2691–2702.
[42] C. Zhang, Z. Wu, J.-W. Li, H. Zhao, G.-Q. Wang, Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality, Int J Antimicrob Agents 55 (2020) 105954.
[43] M. Cancio, R. Ciccocioppo, P.R.M. Rocco, B.L. Levine, V. Bronte, C.M. Bollard, et al., Emerging trends in COVID-19 treatment: learning from inflammatory conditions associated with cellular therapies, Cytotherapy 22 (2020) 474–481.
[44] ClinicalTrials.gov. COVID-19 studies listed on ClinicalTrials.gov. https://ClinicalTrials.gov. Accessed April 13, 2021
[45] J. Galipeau, L. Sensebe, Mesenchymal stromal cells: clinical challenges and therapeutic opportunities, Cell Stem Cell 22 (2018) 824–833.
[46] M.A. Canham, J.D.M. Campbell, J.C. Mountford, The use of mesenchymal stromal cells in the treatment of coronavirus disease 2019, J Transl Med 18 (2020) 359.
[47] Cell and Gene Therapy Catapult. Cell and gene therapy GMP manufacturing in the UK: Capability and capacity analysis. https://ct.catapult.org.uk/sites/default/files/publication/ManufacturingReport2020_PUBLISHED.pdf. Published November 2020. Accessed April 13, 2021
[48] Moderna. Moderna and Vertex establish new collaboration to treat cystic fibrosis using gene editing. https://investors.modernatx.com/news-releases/news-release-details/moderna-and-vertex-establish-new-collaboration-treat-cystic. Published September 16, 202o. Accessed April 13, 2021
[49] FDA. Emergency Use Authorization. www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. Published April 7, 2021. Accessed April 13, 2021
[50] D.M. Smith, E.J. Culme-Seymour, C. Mason, Evolving industry partnerships and investments in cell and gene therapies, Cell Stem Cell 22 (2018) 623–626.
[51] cell&gene. The lasting COVID-19 impact on cell and gene therapy. www.cellandgene.com/doc/the-lasting-covid-impact-on-cell-and-gene-therapy-0001. Published October 30, 2020. Accessed April 13, 2021
[52] FDA. FDA guidance on conduct of clinical trials of medical products during COVID-19 public health emergency. www.fda.gov/media/136238/download. Published January 27, 2021. Accessed April 13, 2021
[53] Y. Hu, E. Tan Su Yin, Y. Yang, H. Wu, G. Wei, et al., CAR T-cell treatment during the COVID-19 pandemic: management strategies and challenges, Curr Res Transl Med 68 (2020) 111–118.
[54] G. Banda, J. Tait, J. Mittra, Evolution of business models in regenerative medicine: effects of a disruptive innovation on the innovation ecosystem, Clin Ther 40 (2018) 1084–1094.
[55] R.P. Harrison, S. Ruck, Q.A. Rafiq, N. Medcalf, Decentralised manufacturing of cell and gene therapy products: Learning from other healthcare sectors, Biotechnol Adv 36 (2018) 345–357.
[56] A.E. Hay, M.C. Cheung, CAR T-cells: costs, comparisons, and commentary, J Med Econ 22 (2019) 613–615.
[57] S. Khozin, A. Coravos, Decentralized trials in the age of real-world evidence and inclusivity in clinical investigations, Clin Pharmacol Ther 106 (2019) 25–27.
[58] E.R. Dorsey, B. Kluger, C.H. Lipset, The new normal in clinical trials: decentralized studies, Ann Neurol 88 (2020) 863–866.
[59] S.J. Balevic, L. Singler, R. Randell, R.J. Chung, M.E. Lemmon, C.P. Hornik, Bringing research directly to families in the era of COVID-19, Pediatric Res 89 (2020) 404–406.
[60] G. Bauer, M. Abou-El-Enein, A. Kent, B. Poole, M. Forte, The path to successful commercialization of cell and gene therapies: empowering patient advocates, Cytotherapy 19 (2017) 293–298.
[61] O.L. Aiyegbusi, K. Macpherson, L. Elston, S. Myles, J. Washington, N. Sungum, et al., Patient and public perspectives on cell and gene therapies: a systematic review, Nat Commun 11 (2020) 6265.
[62] J. Delhove, I. Osenk, I. Prichard, M. Donnelley, Public acceptability of gene therapy and gene editing for human use: a systematic review, Hum Gene Ther 31 (2020) 20–46.
[63] M. Goldman, M. Silva, Reflections on the collaborative fight against COVID-19, Front Med 7 (565) (2020).
[64] D. Patrick, Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension, Value Health 16 (2013) 455–456.
[65] M.R. Bishop, Optimizing administration of CAR T-cell therapy during the COVID-19 pandemic, Clin Adv Hematol Oncol 18 (2020) 400–403.
[66] S. Courbier, R. Dimond, V. Bros-Facer, Share and protect our health data: an evidence based approach to rare disease patients' perspectives on data sharing and data protection – quantitative survey and recommendations, Orphanet J Rare Dis 14 (2019) 175.
[67] A. Fortunato, D.W. Grainger, M. Abou-El-Enein, Enhancing patient-level clinical data access to promote evidence-based practice and incentivize therapeutic innovation, Adv Drug Deliv Rev 136–137 (2018) 97–104.
[68] H.J.S. Dawkins, R. Draghia-Akli, P. Lasko, L.P.L. Lau, A.H. Jonker, C.M. Cutillo, et al., Progress in rare diseases research 2010–2016: an IRDiRC perspective, Clin Transl Sci 11 (2020) 11–20.

[69] M. Elsallab, C.A. Bravery, A. Kurtz, M. Abou-El-Enein, Mitigating deficiencies in evidence during regulatory assessments of advanced therapies: a comparative study with other biologicals, Mol Ther Methods Clin Dev 18 (2020) 269–279.
[70] C.A. Bravery, O. Ball, S. Robinson, EU market authorisation strategy: lessons from the first 22 ATMP submitted to the EMA, Cell Gene Ther Insights 5 (2019) 759–791.
[71] M. Elsallab, B.L. Levine, A.S. Wayne, M. Abou-El-Enein, CAR T-cell product performance in haematological malignancies before and after marketing authorisation, Lancet Oncol 21 (2020) e104–e116.
[72] FDA. Updated information for human cell, tissue, or cellular or tissue-based product (HCT/P) establishments regarding the COVID-19 pandemic. www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/updated-information-human-cell-tissue-or-cellular-or-tissue-based-product-hctp-establishments. Published January 4, 2021. Accessed April 13, 2021
[73] IQWIG. All clinical trial data on Covid-19 medicines and vaccines should be published on the day of marketing authorisation!-Open letter to the European Medicines Agency. www.iqwig.de/en/presse/press-releases/press-releases-detailpage_9953.html. Published May 14, 2020. Accessed April 13, 2021
[74] J. Leahy, C. Hickey, D. McConnell, O. Cassidy, L. Trela-Larsen, M. Barry, et al., Coronavirus disease 2019: considerations for Health Technology Assessment from the National Centre for Pharmacoeconomics Review Group, Value Health 23 (2020) 1423–1426.
[75] C.U. Kunz, S. Jörgens, F. Bretz, N. Stallard, K. Van Lancker, D. Xi, et al., Clinical trials impacted by the COVID-19 pandemic: adaptive designs to the rescue?, Stat Biopharm Res 12 (2020) 461–477
[76] P. Neumann, J.T. Cohen, D.D. Kim, D.A. Ollendorf, Consideration of value-based pricing for treatments and vaccines is important, even in the COVID-19 pandemic, Health Aff 40 (2020) 53–61.
[77] Lambert J. Lynch, Innovative payments for innovative therapies: adopting value-based models in the regenerative medicines advanced therapy sector, Cell Gene Ther Insights 6 (2020) 941–945.
[78] A. Yuasa, N. Yonemoto, M. LoPresti, S. Ikeda, Use of productivity loss/gain in cost-effectiveness analyses for drugs: a systematic review, Pharmacoeconomics 39 (2021) 81–97.
[79] M.C. Nurchis, D. Pascucci, M. Sapienza, L. Villani, F. D'Ambrosio, F. Castrini, et al., Impact of the burden of COVID-19 in Italy: results of disability-adjusted life years (DALYs) and productivity loss, Int J Environ Res Public Health 17 (2020) 4233.
[80] A. Angelis, H. Naci, A. Hackshaw, Recalibrating Health Technology Assessment methods for cell and gene therapies, Pharmacoeconomics 38 (2020) 1297–1308.
[81] M. Abou-El-Enein, G. Bauer, P. Reinke, The business case for cell and gene therapies, Nat Biotechnol 32 (2014) 1192–1193.
[82] M. Senior, Rollout of high-priced cell and gene therapies forces payer rethink, Nat Biotechnol 36 (2018) 291–292.
[83] Emerton. The orphan drug model is in jeopardy: who will lead the charge toward a sustainable future? www.emerton.co/orphan-drug-model/ Accessed April 13, 2021
[84] N. Touchot, M. Flume, The payers' perspective on gene therapies, Nat Biotechnol 33 (2015) 902–904.
[85] CVSHealth. Gene therapy: keeping costs from negating its unprecedented potential. https://payorsolutions.cvshealth.com/sites/default/files/cvs-health-payor-solutions-gene-therapy-keeping-costs-from-negating-its-unprecedented-potential-white-paper-january-2020.pdf. Published January 13, 2020. Accessed April 13, 2021
[86] The World Bank. COVID-19 to plunge global economy into worst recession since World War II. www.worldbank.org/en/news/press-release/2020/06/08/covid-19-to-plunge-global-economy-into-worst-recession-since-world-war-ii. Published June 8, 2020. Accessed April 13, 2021
[87] J.K. Lin, L.S. Muffly, M.A. Spinner, J.I. Barnes, D.K. Owens, J.D. Goldhaber-Fiebert, Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma, J Clin Oncol 37 (2019) 2105–2119.
[88] M. Czech, A. Baran-Kooiker, K. Atikeler, M. Demirtshyan, K. Gaitova, M. Holownia-Voloskova, et al., A review of rare disease policies and orphan drug reimbursement systems in 12 Eurasian countries, Front Public Health 7 (2020) 416.
[89] Gemeinsame Bundesausschuss. G-BA specifies procedures for application-related data collection - Zolgensma gene therapy first case. www.g-ba.de/presse/pressemitteilungen-meldungen/874/. Published July 16, 2020. Accessed April 13, 2021
[90] Haute Autorité de Santé. Zynteglo. www.has-sante.fr/jcms/p_3165706/fr/zynteglo. Published March 26, 2020. Accessed April 13, 2021
[91] Haute Autorité de Santé. Zolgensma. www.has-sante.fr/jcms/p_3224937/fr/Zolgensma. Published December 18, 2020. Accessed April 13, 2021
[92] M. Dabbous, L. Chachoua, A. Caban, M. Toumi, Managed entry agreements: policy analysis from the European perspective, Value Health 23 (2020) 425–433.
[93] E. Hanna, M. Toumi, C. Dussart, B. Borissov, O. Dabbous, K. Badora, et al., Funding breakthrough therapies: a systematic review and recommendation, Health Policy 122 (2018) 217–229.
[94] Anon., Gene therapy's next installment, Nat Biotechnol 37 (2019) 697–707.
[95] D. Coyle, I. Durand-Zaleski, J. Farrington, L. Garrison, J.M. Graf von der Schulenburg, W. Greiner, HTA methodology and value frameworks for evaluation and policy making for cell and gene therapies, Eur J Health Econ 21 (2020) 1421–1437.
[96] M.J. De Castro Lopez, Advanced therapy clinical trials for rare pediatric disorders: key challenges and lessons learned, Cell Gene Ther Insights 6 (2020) 511–515.