RESEARCH PAPER

An analysis of the UK's commercial stem cell clinics

Megan Smith[1], Kate Goodheart[1], Claudia Fryer[1], Tomas Balcytis[1], Peter Wilmshurst[2] and Patricia Murray[1]

[1] Department of Women's and Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool
[2] Royal Stoke University Hospital, Stoke-on-Trent, UK

Submission date: 20 February 2024; Acceptance date: 15 May 2024; Publication date: 6 March 2024

ABSTRACT

Commercial stem cell clinics in the UK are offering therapies of unproven efficacy that have the potential to cause harm. Marketing information used to advertise the therapies is often misleading and prices can be extortionate. Most so-called 'stem cell' therapies are currently exempt from regulations. This needs to be addressed urgently to stop patients from being subjected to financial, physical or psychological harm. To address these problems, we have made several recommendations, which include better education for healthcare professionals, concerted action by regulators and new legislation.

KEYWORDS

stem cells, private clinics, medical research, science policy

Origin of the stem cell industry

Two landmark papers expedited the growth of the global stem cell industry. A paper by Thomson and colleagues in 1998 describing the isolation of pluripotent human embryonic stem cells (hESCs) heralded the era of regenerative medicine (Thomson *et al.*, 1998). Then in 2002, a paper by Jiang and colleagues claimed that mesenchymal cells with similar properties to hESCs could be isolated from bone marrow (Jiang *et al.,* 2002). The ethical dilemmas surrounding hESC research probably explains why Jiang's 2002 paper attracted much attention; in contrast to hESCs, mesenchymal cell procurement does not require human embryos. However, Jiang's results could not be replicated and problems with the data were soon identified (Aldhous and Samuel, 2007; Schneider, 2016). The Jiang paper was finally retracted in June 2024. At the time of retraction it had been cited almost 4,500 times, making it 'the most-cited retracted paper, ever' (Kincaid, 2024).

Following the 2002 Jiang publication, many papers reported that mesenchymal 'stem' cells (MSCs) from various sources, including adipose tissue and umbilical cord, could generate

CONTACT: P.A.Murray@liverpool.ac.uk
ACCEPTING EDITOR: Stuart Macdonald

DOI:10.13169/prometheus.40.1.0007

various specialized cells, including neurons. However, more careful analyses showed that MSCs have limited ability to generate other cell types, and that populations of MSCs contain few, if any, actual 'stem' cells (Caplan, 2017). It has been proposed that MSCs are actually fibroblasts because the properties of these two cell types are indistinguishable (Hematti, 2012). Most academic researchers now refer to MSCs as mesenchymal 'stromal' cells rather than 'stem' cells. But the hype generated by the many erroneous MSC papers helped create a market demand for MSC therapies.

One of the first private clinics was Vannoni's Stamina Foundation in Italy. The clinic claimed MSCs could be converted to neurons and used successfully to treat patients with neurological conditions such as Parkinson's disease (Turone, 2014). The clinic's activities provoked widespread condemnation and Vannoni was eventually convicted for conspiracy and fraud in 2015. Other high-profile clinics that were closed down after harming patients include Germany's X-Cell Centre (Tuffs, 2010), and the Advanced Cell Therapeutics company that operated across many countries, including the UK (Watts, 2006).

Despite widespread media coverage of the harmful practices of rogue stem cell clinics, the stem cell industry has expanded dramatically. In the United States, there were just two stem cell companies in 2009, but by 2021, almost 1,500 had been identified (Turner, 2021). An analysis of the global distribution of private stem cell clinics in 2016 ranked the UK sixth with a total of 16 clinics (Berger *et al.*, 2016). There has been little scrutiny of the stem cell industry in the UK. Erikainen and colleagues found that 106 facilities in the UK were administering 'stem' cell therapies, mostly for orthopaedic conditions and cosmetic enhancement (Erikainen *et al*., 2019). Erikainen's study found that the information on websites tended to be inaccurate. Likewise, Kamel and Smith reported that the majority of UK clinics were presenting misleading information and/or omitting information on potential adverse effects (Kamel and Smith, 2021). We investigated the UK's commercial stem cell clinics in more detail, assessing the health conditions they claim to treat, the range of regenerative therapies advertised, the accuracy of the information provided to prospective patients and the risks such therapies pose. We also examined the role of regulatory authorities.

Overview of the medical conditions being treated by UK clinics

To identify clinics, we undertook Google searches using similar key terms to those used in Erikainen's study (Erikainen *et al.*, 2019), an example being 'UK stem cell clinics'. Because our focus was on the use of unproven stem cell therapies for medical conditions, we excluded clinics offering therapies that have been approved by the UK National Institute for Clinical Excellence (NICE), and those focusing exclusively on cosmetic procedures. We recognize that the 'stem' cell therapies offered for cosmetic enhancement are also problematic, but it was beyond the scope of this paper to include them. We identified 38 clinics (Table 1) offering therapies for medical conditions, which is more than twice the number identified in 2016 (Berger *et al*, 2016). Eighteen of the clinics we identified operated at multiple sites (Table 1). Thirty-five clinics offered stem cell therapies for orthopaedic conditions, the most common being osteoarthritis and sports injuries. Five clinics offered therapies to improve sexual health, sometimes in addition to therapies for orthopaedic conditions. Stem cell treatments for autism, anal fistulas and Lyme disease were exclusively being offered by each of three clinics. One clinic advertised therapies for a wide range of conditions including Parkinson's disease, chronic obstructive pulmonary disease (COPD), diabetes, stroke and cancer (Table 1).

Table 1. UK stem cell clinics

Company name[a] (no. of UK sites)	Website[b]	Type of therapies	Conditions treated
Algocells Ltd (2)	https://web.archive.org/web/20210613121631/https://www.algocells.com/stem-cells/ [June 2021]	bone marrow-derived MSCs; PRP[c]	orthopaedic
Autism Regenerative Centre (1)	https://web.archive.org/web/20191217153848/https://autismregenerativecentre.com/[Jan. 2020]	bone marrow-derived cells (cell type not specified)	autism
Blackberry Clinic Ltd (12)	https://web.archive.org/web/20220903140502/https://www.blackberryclinic.co.uk/ [Sept. 2022]	PRP	orthopaedic
Edinburgh Clinic (1)	https://web.archive.org/web/20220903140721/https://www.edinburghclinic.com/services/orthopaedics/sports-injuries/platelet-rich-plasma-prp-therapy/ [Sept. 2022]	PRP	orthopaedic
Harley Street Skin Clinic (1)	https://web.archive.org/web/20210730040542/https://www.harleystreetskinclinic.com/en/treatment-area/regenerative-medicine/ [July 2021]	adipose and umbilical cord tissue-derived MSCs (provided by LifePlus SCT)	orthopaedic; COPD; diabetes; Parkinson's; stroke; cancer; MS; erectile dysfunction; cosmetic
Harley Street Hospital (1)	https://web.archive.org/web/20220903142733/https://theharleystreethospital.co.uk/spinal-stem-cell-treatment/ [Sept. 2022]	adipose-derived stem cells; PRP	orthopaedic; vaginal atrophy
Harley Street Specialist Hospital (1)	https://web.archive.org/web/20220903142733/https://theharleystreethospital.co.uk/spinal-stem-cell-treatment/ [Sept. 2022]	bone marrow concentrate; PRP	orthopaedic
Highgate Private Hospital LLP (1)	https://web.archive.org/web/20220903143124/https://www.highgatehospital.co.uk/services/orthopaedic-treatment/sports-injuries/non-surgical-orthopaedic-treatments/stem-cell-therapy/ [Sept 2022]	bone marrow, blood or adipose-derived stem cells, administered with a scaffold	orthopaedic
HR Orthopaedics (1)	https://web.archive.org/web/20210515134444/https://www.hrorthopaedics.co.uk/hips/stem-cell-therapy/ [May 2021]	bone marrow concentrate (containing stem cells); PRP	orthopaedic
International Andrology London (1)	https://web.archive.org/web/20220903143617/https://london-andrology.co.uk/news/stem-cell-treatment-for-erectile-dysfunction/ [Sept. 2022]	bone marrow, blood or adipose-derived stem cells	erectile dysfunction
Kent MusculoSkeletal Clinic (1)	https://web.archive.org/web/20220903163418/https://kentmskclinic.co.uk/services/ultrasound-guided-prp-injections/ [Sept. 2022]	PRP	orthopaedic
Kliniken (1)	https://web.archive.org/web/20220903185134/https://www.kliniken.co.uk/joint/arthroscopy/ [Sept. 2022]	adipose-derived stem cells	orthopaedic; cosmetic
LifePlus Stem Cell Technologies LLP (1)	https://web.archive.org/web/20210101100943/https://lifeplusstemcells.com/ [Jan. 2021]	adipose and umbilical cord tissue-derived MSCs	orthopaedic; cosmetic

(Continued)

Table 1. (Continued)

Company name[a] (no. of UK sites)	Website[b]	Type of therapies	Conditions treated
London Bridge Plastic Surgery (C&M Health Ltd) (1)	https://web.archive.org/web/20220903183421/https://www.lbps.co.uk/stem-cell-therapy/joint-osteoarthritis/ [Sept. 2022]	adipose-derived stem cells called Orthoskill	orthopaedic; cosmetic
London Orthopaedic Clinic (1)	https://web.archive.org/web/20220903163925/https://www.londonorthopaedic.com/prp-injections/ [Sept. 2022]	PRP	orthopaedic
London Stem Cell Centre (2)	https://web.archive.org/web/20220811153323/https://londonstemcellcentre.com/ [Aug. 2022]	bone marrow concentrate (containing MSCs); PRP	orthopaedic
London and Sports Injury Clinic at 108 Harley Street (1)	https://web.archive.org/web/20220811153804/https://108harleystreet.co.uk/for-patients/sports-injury/what-is-the-lipogems-method/ [Aug. 2022]	Lipogems	orthopaedic
Manchester Hip Clinic (Fehily Orthopaedics) (2)	https://web.archive.org/web/20220903164616/https://manchesterhipclinic.com/stem-cell-therapy/ [Sept. 2022]	bone marrow-derived MSCs	orthopaedic
Medica Stem Cells (MSC UK) (6)	https://web.archive.org/web/20220903170305/https://medicastemcells.com/iv-cell-therapy/ [Sept. 2022]	adipose-derived cells; IV cell therapy; PRP	orthopaedic; erectile dysfunction; cosmetic and 'many more conditions'
Midland Knee Protect Clinic (1)	https://web.archive.org/web/20210920234023/https://www.midlandkneeprotectclinic.co.uk/about [Sept. 2021]	Lipogems; PRP	orthopaedic
Miller Orthopaedics (2)	https://web.archive.org/web/20220903172238/https://www.millerorthopaedics.co.uk/ [Sept. 2022]	PRP	orthopaedic
Orthopaedic Hip and Knee Solutions Ltd (1)	https://web.archive.org/web/20210805181642/http://www.ohks.co.uk/stemcell-implantation.php [Sept. 2022]	bone marrow-derived stem cells; PRP	orthopaedic
Osom Care LLP[c] (1)	https://web.archive.org/web/20220903173153/https://www.osomcare.co.uk/treatments-manchester/ [Sept. 2022]	PRP	orthopaedic
Pall Mall Medical Ltd (4)	https://web.archive.org/web/20220903173502/https://www.pallmallmedical.co.uk/doctors/stem-cell/ [Sept. 2022]	bone marrow-derived stem cells	orthopaedic
Regenerative Clinic Ltd (6)	https://web.archive.org/web/20220515200505/https://www.theregenerativeclinic.co.uk/stem-cell-therapy-treatment-explained/ [May 2022]	bone marrow concentrate (containing stem cells); Lipogems PRP; peripheral blood monocytes	orthopaedic; gynaecological conditions; anal fistula
Regenerate Myself (2)	https://web.archive.org/web/20220410142051/https://www.regeneratemyself.co.uk/ [Apr. 2022]	Lipogems; PRP	orthopaedic
Regenerative Therapy Centre Ltd[c] (1)	https://web.archive.org/web/20220903175956/https://www.regenerativetherapycentre.co.uk/treatments/mesenchymal-signalling-cells/ [Sept. 2022]	bone marrow and peripheral blood-derived MSCs; PRP	orthopaedic

Company name[a] (no. of UK sites)	Website[b]	Type of therapies	Conditions treated
Regenesis Orthobiologics Ltd[c] (4)	https://web.archive.org/web/20211028023628/https://www.regenesiss.co.uk/ [Oct. 2021]	adipose-derived MSCs; bone marrow-derived 'hematopoietic mesenchymal mononuclear cells'	orthopaedic
Regenext Clinic[c] (1)	https://web.archive.org/web/20220903180338/https://www.regenextclinic.com/stem-cell-therapy/ [Sept. 2022]	adipose- derived and bone marrow-derived stem cells	orthopaedic
Rogers Regenerative Medicine Group Ltd (2)	https://web.archive.org/web/20220712210845/https://regenortho.com/ [July 2022]	adipose-derived stem cells; PRP	orthopaedic
Spire Healthcare (6)	https://web.archive.org/web/20220903180750/https://www.spirehealthcare.com/treatments/blood-tests/stem-cell-therapy/ [Sept. 2022]	bone marrow or blood-derived MSCs	orthopaedic
Sports Orthopaedic Specialist (2)	https://web.archive.org/web/20220903181042/https://www.sportsorthopaedicspecialist.co.uk/ [Sept. 2022]	PRP	orthopaedic
Stem Cell Science (The Academy of Regen Med) (2)	https://web.archive.org/web/20220903181206/https://www.stemcellscience.co.uk/ [Sept. 2022]	adipose-derived stem cells; PRP	orthopaedic; cosmetic
Stemvita Ltd (2)	https://web.archive.org/web/20220313193149/https://www.stemvita.co.uk/ [Mar. 2022]	adipose-derived stem cells (including IV injections); PRP	Lyme disease; hair loss; osteoarthritis; rheumatoid arthritis
Total Orthopaedics Ltd (15)	https://web.archive.org/web/20211028204824/https://www.totalorthopaedics.london/treatments/biological-treatments/[Oct. 2021]	bone marrow concentrate (containing stem cells); Lipogems	orthopaedic
UK Orthobiologics Clinic Ltd (2)	https://web.archive.org/web/20211019180359/https://www.orthobiologicsclinic.co.uk/stem-cell-therapy-macclesfield-cheshire-manchester.html [Oct. 2021]	bone marrow concentrate (containing stem cells); adipose-derived MSCs; PRP	orthopaedic
Villar Bajwa Ltd (1)	https://web.archive.org/web/20210515120832/http://villarbajwa.com/stem-cell-therapy.shtml [May 2021]	bone marrow concentrate (containing stem cells)	orthopaedic
Women's Health Clinic Ltd (previously The Genesis clinic) (10)	https://web.archive.org/web/20220812092616/https://www.thewomenshealth.clinic/specialist-gynaecology/ [Aug. 2022]	PRP (injected to the clitoris and/or vagina)	sexual disorders

[a] Thirty-eight clinics were identified, with some operating across multiple sites.

[b] Links are for clinic websites that were active in Sept. 2022 and archived on the date indicated.

[c] PRP (platelet-rich plasma) has been approved by NICE for early-stage knee osteoarthritis, but only with special arrangements for clinical governance, consent and audit or research. We included PRP because most clinics were advertising beyond this narrow remit.

[d] Lipogems is a device for generating mechanically fragmented adipose tissue that is reported to contain MSCs.

[e] Osom Care, Regenerative Therapy Centre, Regenesis Orthobiologics and Regenext have the same director.

LifePlus STC = LifePlus Stem Cell Technologies; COPD = chronic obstructive pulmonary disease; MS = multiple sclerosis

The types of stem cell and regenerative medicine therapies on offer

After establishing the number of clinics and the conditions being treated, we considered the types of therapies offered. In addition to therapies marketed as 'stem cells', we included biologics that are typically badged as 'regenerative'. Most clinics were offering autologous therapies derived from the patient's own bone marrow, adipose tissue or peripheral blood. The cell-based therapies are typically referred to as 'mesenchymal stem cells' or just 'stem cells'. Five clinics offered 'Lipogems®', comprising mechanically fragmented adipose tissue, claimed to contain MSCs. Twenty-three clinics offered 'platelet rich plasma (PRP)', which is prepared by spinning down peripheral blood to separate the platelets from other cell types. A typical claim made is that PRP stimulates the regeneration of tendons, ligaments and cartilage.

Although most clinics were marketing autologous therapies, two clinics were offering an allogeneic therapy comprising umbilical cord-derived MSCs (UC-MSCs). Because these therapies are allogeneic, and are administered without anti-rejection medication, all injected cells are likely to be dead within a short time frame as a result of rejection by the recipient. One of these clinics was focusing on orthopaedic conditions and cosmetic enhancement, but was also providing the UC-MSCs to the other clinic, which advertised the cells as a treatment for various incurable diseases, with prices starting from £20,000.

What is the evidence that the therapies being offered are safe and effective?

Next, we examined the evidence supporting the use of the different 'stem' cell therapies for the conditions the clinics treat. It would be beyond the scope of this paper to discuss all conditions, so we have focused on therapies for COPD and Parkinson's disease, and MSC treatments for osteoarthritis, which are offered by most UK 'stem' cell clinics. For COPD, one clinic's website states: 'Stem cell treatment is the closest you will get to a lung transplant due to its ability to regrow damaged tissue'. The evidence to support this statement is not robust. The American Thoracic Society states: 'there is no reliable evidence that stem cell treatments are effective for any lung disease' (American Thoracic Society, 2017). A possible risk is that the MSCs could lead to pulmonary embolism (Moll *et al.*, 2022). This is a potentially lethal risk, particularly for patients with COPD whose pulmonary function and pulmonary vascular reserve are already compromised, and pulmonary artery pressures are already increased. When MSCs are used in well-controlled clinical trials, their safety profile is good because the medical practitioners administering them are aware of the potential side effects. However, in poorly regulated environments, patients are at considerable risk. For instance, thromboembolism has been reported in two cases following intravenous administration of umbilical cord tissue-derived MSCs (Wu *et al.*, 2017), and a patient died in a Japanese clinic from pulmonary embolism (Cyranoski, 2010).

As for Parkinson's disease, one clinic stated that stem cells with the ability to make dopaminergic neurons reside in bone marrow, fat and umbilical cord tissue, and referred to the umbilical cord cells as an 'embryonic stem cell treatment'. First 'stem' cells found in bone marrow, fat and umbilical tissue cannot generate dopaminergic neurons. Second, it is incorrect to refer to umbilical tissue as an 'embryonic stem cell treatment'. Embryonic stem cells are pluripotent cells that are present only in pre-implantation embryos. They are not found in umbilical cords. Misrepresentation of cord cells as an embryonic stem cell-based therapy has the potential to mislead patients. Those with incurable neurological diseases are particularly vulnerable. A recent survey in the US found that 64.5% of neurologists reported that one or more of their patients had received an unproven stem cell therapy (Julian *et al.*, 2020). Of concern, 24.6% reported that their patients had experienced complications that related to the therapy; these included infection, stroke and death.

Clinics offering regenerative therapies for osteoarthritis, also known as 'orthobiologics', typically claim that the treatments can delay or prevent the need for joint replacement. To assess this claim, we analysed an extensive list of research publications compiled by one particular clinic and portrayed as providing the clinical evidence that the treatments worked. Of the 90 papers listed, only six reported the results of randomized controlled trials (RCTs), and all claimed efficacy of MSCs in osteoarthritis (Jo *et al*., 2014; Lamo-Espinosa *et al.*, 2016; Matas *et al.*, 2019; Freitag *et al.*, 2019; Lee *et al*., 2019; Bastos *et al.*, 2020). In all six studies there were fewer than 20 patients per group, giving the studies a low statistical power. In four of these studies, there was a financial link between some authors and the company providing the cells, raising concerns about potential bias. The clinic did not list papers that suggested MSCs were not effective, such as a systematic review that concluded there was low confidence in MSC efficacy (Xing *et al.*, 2018), and a more recent review that found the certainty of the evidence for efficacy was low to very low (Wiggers *et al.*, 2021).

Given the unconvincing evidence of efficacy of regenerative medicine therapies for osteoarthritis, it is difficult to understand why UK clinics are allowed to sell them to patients for profit. A paper by Murray and colleagues highlights the problems posed by unproven stem cell therapies for orthopaedic conditions, noting that the administration of adipose-derived MSCs into the knee joint can cause pain and swelling in up to 37% of patients (Murray *et al.*, 2020). More serious examples of complications include two UK patients with life-threatening thrombosis after a regenerative medicine product was injected into their hip joints, and another patient who developed an infection which made their subsequent hip replacement much more complicated (Naish, 2020). The British Orthopaedic Association recently published a document emphasising that there is no medical evidence that orthobiologics result in any structural improvement or creation of new tissue, such as articular cartilage, and that any treatment that involved injecting a substance into a joint is not without risk (British Orthopaedic Association, 2022).

Most stem cell therapies offered by UK clinics are classed as 'non-homologous', meaning the cells are expected to behave differently in their new environment from the way they behaved in the tissue from which they were derived. In the US, the non-homologous use of cell therapies requires pre-marketing approval from the US Food and Drug Administration (FDA). To lawfully market such products, companies should obtain a biologics licence, which requires demonstrating the safety, purity and potency of the cells to the FDA (FDA, 2020). In the US, several patients have experienced serious complications, including septicaemia and sudden blindness following administration of 'stem' cell therapies (Turner, 2021). A problem for the FDA is that there are now so many clinics marketing non-compliant cell therapy products in the US that it may be impossible for the regulator to take enforcement action against them all. In the UK, relevant authorities, such as the Medicines and Healthcare products Regulatory Authority (MHRA), the Human Tissue Authority (HTA) and the Care Quality Commission (CQC) appear to have no position on the non-homologous use of unproven 'stem' cell therapies (Naish, 2020). Although patients have suffered physical and financial harm, effective regulation is lacking. Our most troubling finding is that two UK clinics advertised unlicensed and unproven *allogeneic* cell therapies (UC-MSCs) for non-homologous use, even though Regulation 279 of the Human Medicines Regulations 2012 prohibits advertising unlicensed medicines. Websites of both clinics stated, as a unique selling point, that appropriate licences from the HTA and MHRA were in place. One of the clinics claimed it provided 'the UK's first quantifiable and quality assured stem cells'. The cells used by both clinics were being manufactured under an MHRA 'specials' licence. The UK's General Medical Council (GMC) requires that unlicensed medicines should be prescribed only to meet the specific needs of an individual patient, and the prescribing doctor should be satisfied that there is sufficient evidence to demonstrate the medicine's safety and efficacy (GMC, 2021). It appears that this requirement was overlooked by practitioners administering UC-MSC therapies at commercial clinics because there is no robust evidence from Phase III RCTs to show that UC-MSCs are effective in the treatment of any medical condition.

The role of UK authorities in regulating 'stem' cell clinics

Many of the UK clinics were undertaking activities that had the potential to mislead and/or cause financial, physical or psychological harm to patients. These included (i) overstating the potential benefits of the treatments and omitting possible risks; (ii) unsupported statements about the nature and provenance of the therapies and how they behave following administration; (iii) breaching Regulation 279 of the Human Medicines Regulations 2012 by advertising unproven 'stem' cell therapies under an MHRA 'specials' licence; (iv) administering UC-MSCs for profit without obtaining fully informed consent from cord donors; (v) medical doctors operating outside their area of expertise (e.g., an aesthetic practitioner treating patients with COPD); (vi) patients being charged extortionate prices for unproven treatments that cannot possibly benefit them and have the potential to be harmful.

Collectively, the above activities fall within the remit of five different UK authorities: the HTA, MHRA, CQC, GMC and the Advertising Standards Authority (ASA) (Panel 1). Only a few clinics were engaged in all six activities, but the majority appeared to be engaged in misleading advertising and were offering unproven treatments that have the potential to harm. A $US5.1 million judgement has been secured against a New York clinic for 'scamming patients out of thousands through false advertising' (Office of the New York Attorney General, 2021). The Attorney General in the case stated that 'misleading New Yorkers who are seeking treatment for serious and potentially life-threatening medical conditions is unlawful and an affront to our societal values'. In the UK, one clinic has been rebuked by the ASA for publishing a misleading and unsubstantiated advertorial about regenerative therapies for arthritis (ASA, 2020), but as far as we are aware, no UK clinics have been prosecuted for false advertising.

Panel 1: Goals of relevant organizations

HTA

To ensure that human tissue and organs are used safely and ethically, and with proper consent.

MHRA

To protect and promote public health and patient safety by ensuring that medicines and medical devices meet appropriate standards of safety, quality, performance and effectiveness.

To regulate the promotion of medicinal products and ensure that advertising complies with the legislation, and (using statutory powers) take any necessary action, including the enforcement of criminal and/or civil sanctions when breaches have been identified

ASA

To keep UK advertising legal, decent, honest and truthful.

CQC

To make sure health and social care services provide people with safe, effective, compassionate, high-quality care.

GMC

To protect patient safety and improve medical education and practice across the UK.

In January 2022, the corresponding author (Patricia Murray) reported the two clinics offering allogeneic therapies to the ASA, MHRA and HTA. This was because of concerns for patient safety, but also to see how the regulators would respond. The most responsive regulator was the ASA, which said it had discussed the complaint with the MHRA, and that the MHRA was conducting its own investigation in conjunction with other regulatory bodies (presumably the HTA). The ASA indicated that, if there was anything it could do beyond the work of the MHRA, it would be happy to take up the complaint again. The MHRA and HTA were not very forthcoming in explaining how they would handle the complaint. Nevertheless, shortly after submitting the complaint, the website of one of the clinics went off-line, and most of the information relating to stem cells on the website of the other clinic was removed.

One of the clinics and/or its clinical lead was also reported to the CQC and GMC, respectively. These regulators were informed that seriously ill patients were being administered inappropriate 'stem' cell therapies at extortionate prices, therapies likely to be of no benefit and which could be harmful. The CQC said it was satisfied that the clinic was operating within CQC regulations. The GMC advised contacting the CQC as it felt the CQC would be best placed to assess the treatments being offered. Because the GMC appeared to have overlooked key elements of the complaint, an appeal was submitted. According to the GMC website, the clinical lead has a previous GMC finding of misconduct for poor clinical care of a patient.

The response of most UK authorities to the complaints highlights the inadequacy of the regulations and their enforcement in regard to UK stem cell clinics. The only authority that responded appropriately was the ASA. Although the MHRA and HTA seemed to be investigating, the complainant was not informed. It is also unlikely that the results of any investigation or enforcement action will be publicly disclosed, so prospective patients will also be uninformed. Most worrying were the responses of the CQC and GMC, whose main aim is to ensure patient safety (Panel 1). Both of these authorities were happy to overlook questionable practices that had potential to harm patients. Unfortunately, such inertia serves to embolden practitioners who are engaged in exploitative and potentially harmful activities.

An issue that our investigation revealed is that none of the UK regulators is addressing the problem of unproven 'stem cell' therapies being offered to patients for profit. Most clinics are marketing autologous therapies that are prepared and injected in a single session. This practice is not regulated. The problems this poses were highlighted in a media article in 2020 (Naish, 2020), which included the following quote from the MHRA on autologous 'stem' cell therapies: 'we are currently consulting with relevant stakeholders and reviewing their submissions'. The result of the consultation has not been made public. The article concludes with the question 'How many more people must fall victim before UK regulators finally act?' Now that UK stem cell clinics are expanding into treatments for serious conditions, such as Parkinson's disease, COPD and autism, this question is all the more urgent.

Time for action

Medical regulators have a poor record for dealing with doctors who exploit desperate patients by providing bogus treatments, usually for a high price. What distinguishes the claims for most bogus treatments from the false therapeutic claims for the regenerative properties of MSCs is that the former deceive gullible patients, whereas the claims about MSCs often deceive medical and scientific experts as well. For example, in 2008 the *Lancet* published a paper in which the authors claimed to have tissue-engineered an airway using 'mesenchymal stem-cell-derived chondrocytes that had been cultured from cells taken from the recipient' (Macchiarini *et al.*, 2008). It took 15 years before the falsified paper was retracted by the *Lancet*. During those years its authors were employed by prestigious academic institutions and were awarded millions of pounds from grant bodies to extend the research. Further false papers were published and patients died when similar operations were performed (Schneider, 2017; Schneider *et al.*, 2022).

Apart from the harm done to patients, unsupported claims about stem cell therapies and their inappropriate use at private clinics risk bringing the field of regenerative medicine into disrepute. Any potential good that bona fide stem cell therapies may do in the future is being overshadowed by the actual harm being done to patients now. Moreover, when patients are harmed, it is generally the UK's National Health Service that has to step in to remedy the situation, creating an additional burden on already over-stretched services. To tackle the problems posed by stem cell clinics, we have made seven key recommendations (Panel 2), which include better education for healthcare professionals, concerted action by regulators and new legislation.

Panel 2: Recommendations

1. More education

The global stem cell industry is expanding year-on-year. It is important that healthcare professionals have greater knowledge of stem cell biology and the problems posed by unproven therapies to inform their own practice and provide accurate information to patients. We recommend that the GMC and the Medical Royal Colleges require that undergraduate and postgraduate training include teaching on stem cell biology and the stem cell industry.

2. Autologous treatments should be regulated

Autologous stem cell and regenerative therapies administered as part of a single surgical procedure are currently exempt from regulation. This has led to a rapid expansion in the number of clinics offering these types of unproven therapies. We recommend that non-homologous autologous therapies should be regulated much more strictly. Stem cell treatments that are not approved as treatments by Medical Royal Colleges, NICE and/or regulators should not be used except in registered randomized clinical trials. This should apply even when autologous stem cell treatments are performed as a single procedure.

3. The inappropriate use of MHRA 'specials' licences should be prohibited

Our investigation identified two clinics that were advertising autologous and allogeneic therapies under a 'specials' licence, which is in breach of Regulation 279 of the Human Medicines Regulations 2012. It should be unlawful to administer unproven and potentially harmful therapies to patients for profit via a 'specials' licence, irrespective of whether they are being advertised. At present, it appears that the MHRA is willing to grant 'specials' licences, provided the manufacturing process is of an acceptable quality. We recommend that, before granting a 'specials' licence for manufacturing ATMPs (advanced therapy medicinal products), a robust evaluation is undertaken to assess the appropriateness of the therapy. It should be a criminal offence to use 'specials' licences to circumvent the requirement for marketing authorization.

4. Concerted action needed by regulators

The regulation of stem cell clinics is fragmented, with different authorities being responsible for regulating specific activities. There are particular concerns when doctors work in private practice because of the possibility for financial rewards to influence treatments provided, especially when doctors work solely in private practice, or provide different clinical services in their private practice from those provided in their NHS practice. This is because NHS practice generally has greater oversight. We recommend the establishment of a joint regulatory committee comprising representatives of the ASA, HTA, MHRA and CQC to regulate private stem cell clinics, review complaints and implement sanctions.

5. Greater transparency

The results of investigations into stem cell companies are not always made public by some regulators, even when improprieties are discovered. Members of the public should have access to this information. We recommend that improprieties be registered on a public database.

6. Reporting concerns

Many stem cell companies are publishing false and misleading information on their websites about stem cell therapies. This false information is rarely challenged. Experts in the field need to be more proactive about reporting false advertising to the ASA and MHRA.

7. Parliamentary inquiry

We recommend that a joint inquiry be conducted by the Science and Technology, and Health and Social Care Select Committees to assess the problems with UK stem cell clinics and make recommendations on how the industry might be regulated better to protect patients.

Acknowledgements

Most of the authors have been involved in stem cell research and some have been involved in reporting unethical misconduct by doctors. Megan Smith, Kate Goodheart and Claudia Fryer have contributed equally to the research.

References

Advertising Standards Authority (2020) 'ASA ruling on The Regenerative Clinic Ltd', 5 August, available at https://www.asa.org.uk/rulings/the-regenerative-clinic-ltd-a20-1056974-the-regenerative-clinic-ltd.html (accessed February 2024).

Aldhous, P. and Samuel, E. (2007) 'Fresh questions on stem cell findings', *New Scientist*, 24 March, pp.12–13.

American Thoracic Society (2017) 'Unproven stem cell treatments for lung disease – an emerging public health problem', *American Journal of Respiratory and Critical Care Medicine*, 195*,* pp.13–14.

Bastos, R., Mathias, M., Andrade, R. … Espregueira-Mendes, J. (2020) 'Intra-articular injection of culture-expanded mesenchymal stem cells with or without addition of platelet-rich plasma is effective in decreasing pain and symptoms in knee osteoarthritis: a controlled, double-blind clinical trial', *Knee Surgery, Sports Traumatology, Arthroscopy,* 28, pp.1989–99.

Berger, I., Ahmad, A., Bansal, A. … Rasko, J. (2016) 'Global distribution of businesses marketing stem cell-based interventions', *Cell Stem Cell*, 19, pp.158–62.

British Orthopaedic Association (2022) *Injectable Orthobiologic Treatments for Osteoarthritis*, 1 March, available at https://www.boa.ac.uk/resources/injectable-orthobiologic-treatments-for-osteoarthritis.html (accessed February 2024).

Caplan, A. (2017) 'Mesenchymal stem cells: time to change the name!', *Stem Cells Translatioanl Medicine*, 6, 6, pp.1445–51.

Cyranoski, D. (2010) 'Korean deaths spark inquiry', *Nature*, 468, 23 November, p.485.

Erikainen, S., Couturier, A. and Chan, S. (2019) 'Marketing experimental stem cell therapies in the UK: biomedical lifestyle products and the promise of regenerative medicine in the digital era', *Science Cult* (London), 29, pp.219–44.

Food and Drug Administration (2020) *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. Guidance for Industry and Food and Drug Administration Staff*, July, available at https://www.fda.gov/media/109176/download (accessed February 2024).

Freitag, J., Bates, D., Wickham, J. … Boyd, R. (2019) 'Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial', *Regenerative Medicine,* 14, pp.213–30.

GMC (2021) 'Prescribing unlicensed medicines' April, para 105, available at https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines# (accessed February 2024).

Hematti, P. (2012). 'Mesenchymal stromal cells and fibroblasts: a case of mistaken identity?', *Cytotherapy.* 14, 516–21.

Jiang, Y., Jahagirdar, B., Reinhardt, R. … Verfaillie, C. (2002) 'Pluripotency of mesenchymal stem cells derived from adult marrow', *Nature*, 418, pp.41–9.

Jo, C., Lee, Y., Shin, W. … Yoon, K. (2014) 'Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial', *Stem Cells*, 32, pp.1254–66.

Julian, K., Yuhasz, N., Rai, W., Salerno, J. and Imitola, J. (2020) 'Complications from "stem cell tourism" in neurology', *Annals of Neurology,* 88, pp.661–8.

Kamel, S. and Smith, K. (2021) 'Stem-cell clinics in the UK: a web-based study', *Regenerative Medicine*, 16, pp.1029–36.

Kincaid, E. (2024) 'Nature retracts highly cited 2002 paper that claimed adult stem cells could become any type of cell', *Retraction Watch*, 18 June, available at https://retractionwatch.com/2024/06/18/nature-retracts-highly-cited-2002-paper-that-claimed-adult-stem-cells-could-become-any-type-of-cell/ (accessed June 2024).

Lamo-Espinosa, J., Mora, G., Blanco, J. … Prósper, F. (2016) 'Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in

the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II)', *Journal of Translational Medicine*, 14, 246*,* pp.1–9.

Lee, W., Kim, H., Kim, K., Kim, G. and Jin, W. (2019) 'Intra-articular injection of autologous adipose tissue-derived mesenchymal stem cells for the treatment of knee osteoarthritis: a phase IIb, randomized, placebo-controlled clinical trial', *Stem Cells Translational Medicine*, 8, pp.504–11.

Macchiarini, P., Jungebluth, P., Go, T., Asnaghi, M. … Birchall, M. (2008) 'Clinical transplantation of a tissue-engineered airway', *Lancet*. 372, 9655, pp.2023–30.

Matas, J., Orrego, M., Amenabar, D., Infante, C. … Espinoza, F. (2019) 'Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial', *Stem Cells Translational Medicine*, 8, pp.215–24.

Moll, G., Ankrum, J., Olson, S. and Nolta, J. (2022) 'Improved MSC minimal criteria to maximize patient safety: a call to embrace tissue factor and hemocompatibility assessment of MSC products', *Stem Cells Translational Medicine,* 11, pp.2–13.

Murray, I., Chahla, J., Frank, R. … Dragoo, J. and Members of the Biologics Association (2020) 'Rogue stem cell clinics', *Bone and Joint Journal*, 102-B, 2, pp.148–54.

Naish, J. (2020) 'Why are patients STILL at risk from stem cell jabs? It's the trendy treatment pushed by UK clinics as the solution to everything from arthritis to autism. But many experts are concerned that it remains unregulated', *Daily Mail*, 31 August, available at https://www.dailymail.co.uk/health/article-8682725/Why-patients-risk-stem-cell-jabs.html (accessed February 2024).

Office of the New York Attorney General (2021) 'Attorney General James secures $5.1 million judgment against New York City stem cell clinic for scamming patients out of thousands through false advertising', 21 November, available at https://ag.ny.gov/press-release/2021/attorney-general-james-secures-51-million-judgment-against-new-york-city-stem (accessed February 2024).

Schneider, L (2016) 'The stem cell faith healers, or magic inside your bone marrow', *For Better Science*, 26 April, available at https://forbetterscience.com/2016/04/26/the-stem-cell-faith-healers-or-magic-inside-your-bone-marrow/ (accessed February 2024).

Schneider, L. (2017) 'Macchiarini's trachea transplant patients – the full list', *For Better Science,* 16 June available at https://forbetterscience.com/2017/06/16/macchiarinis-trachea-transplant-patients-the-full-list/ (accessed June 2024).

Schneider, L., Murray, P., Levy, R. and Wilmshurst, P. (2022) 'Time to retract *Lancet* paper on tissue engineered trachea transplants', *BMJ-British Medical Journal*, 376, p.o498.

Thomson, J., Itskovitz-Eldor, J., Shapiro, S. … Jones, J. (1998) 'Embryonic stem cell lines derived from human blastocysts', *Science*, 282, pp.1145–7.

Tuffs, A. (2010) 'Stem cell treatment in Germany is under scrutiny after child's death', *BMJ-British Medical Journal*, 341, p.c6203.

Turner, L. (2021) 'The American stem cell sell in 2021: US businesses selling unlicensed and unproven stem cell interventions', *Cell Stem Cell*, 28, pp.1891–5.

Turone, F. (2014) 'Italian doctors behind an unproved stem cell therapy face prosecution', *BMJ-British Medical Journal*, 348, p.g3163.

Watts, S. (2006) 'Stem cell treatment warning', *BBC Newsnight*, 30 August, available at http://news.bbc.co.uk/1/hi/programmes/newsnight/5299306.stm (accessed February 2024).

Wiggers, T., Winters, M., Van den Boom, N., Haisma, H. and Moen, M. (2021) 'Autologous stem cell therapy in knee osteoarthritis: a systematic review of randomised controlled trials', *British Journal of Sports Medicine*, 55, pp.1161–9.

Wu, Z., Zhang, S., Zhou, L., Cai, J. … Li, D. (2017) 'Thromboembolism induced by umbilical cord mesenchymal stem cell infusion: a report of two cases and literature review', *Transplantation Proceedings*, 49, pp.1656–8.

Xing, D., Wang, Q., Yang, Z., Hou, Y. … Lin, J. (2018) 'Mesenchymal stem cells injections for knee osteoarthritis: a systematic overview', *Rheumatology International*, 38, pp.1399–1411.