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# A Lookback Investigation of United Kingdom Residents Who Received Unscreened Stem Cells

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## Abstract

**Background:** Research into stem cell therapy to treat many chronic conditions is ongoing, and has triggered a 'stem cell tourism' phenomenon whereby individuals travel to receive unproven therapies. The Health Protection Agency (HPA) (now Public Health England was informed in 2007 of an incident where United Kingdom (UK) residents had received unscreened stem cells in the Republic of Ireland. A patient-notification exercise (lookback) was launched to test recipients for blood-borne infections.

**Methods:** Patients were identified, located and contacted via their physicians. After obtaining patient consent, serum samples were obtained from patients and sent for testing at the HPA. Results were returned to patients and their physicians.

**Results:** Of 59 UK residents who received stem cells in the Republic of Ireland, 42 consented to testing. Of these 59 individuals, forty were confirmed to be negative for all infections; two patients required further testing to assess initially reactive/equivocal results, but declined, and twelve patients declined testing or were untraceable.

**Conclusions:** Stem cell tourism exposes vulnerable patients to unnecessary risks and demonstrates a clear misalignment of public/patient understanding and scientific findings. It is of major public health importance to question the source and donor screening of stem cells when unregulated 'treatments' are offered.

**Keywords:** Stem cells; Look back; Medical tourism; Stem cell tourism; Blood borne viruses; Public health

## Introduction

Medical tourism, travelling (sometimes overseas) to access health care, may be undertaken for a variety of medical conditions [1-3]. Early-stage research into stem cells has triggered the rise in a phenomena referred to as "stem cell tourism" where individuals with chronic medical conditions travel to receive unproven stem cell 'treatments' outside of the regulatory environment [4-13]. While some stem cell-based treatments are established as standard therapies for a limited number of conditions including leukaemia, their complexity means that rigorous research into their therapeutic use in new areas is still needed [1,4]. They have been implicated as having the potential for treating and curing a number of chronic diseases, including degenerative diseases such as multiple sclerosis (MS) and Parkinson's disease. However, none of these many possible interventions have yet been proven to be both safe and effective in humans [5,9,14-18].

Stem cells are the body's source of cell and tissue renewal and have varying potentials for differentiation. Recent research surrounds multipotent cells which can become several limited cell types (these depend on the parent cell) and pluripotent cells which have the potential to become any type of adult or fetal cell [9,15,16]. Multipotent cells include hematopoietic stem cells (HSCs) found in the bone marrow, the liver, peripheral blood, placental or umbilical cord blood (UCB); neural stem cells (NSCs) found in brain tissue and the spinal cord; and mesenchymal stem cells (MSCs) usually obtained from UCB or bone marrow [9,15]. Pluripotent cells include embryonic stem cells (ESCs) harvested from embryos, and induced pluripotent cells (iPS) from several somatic cell types [9,15].

In 2007, the Health Protection Surveillance Centre (HPSC) of the Republic of Ireland (IRL), informed the Health Protection Agency (HPA) of a general practitioner's (GP) administration of an unauthorised stem cell treatment to a number of patients, some of whom were UK-residents. When the Irish Medicines Board became aware of the treatments, the GP was asked to cease all practices involving administration of stem cells, and an investigation was launched.

The stem cell recipients had various chronic conditions, including multiple sclerosis (MS), and had paid varying sums of money to receive the treatment. The HPA was informed that each patient usually received one or more subcutaneous injections of a single vial containing 1.5 million stem cells, believed to be of umbilical cord origin. However, the origin and quality of the stem cells could not be determined or verified. Reports in the media at the time suggested that the stem cells were intended for research purposes only and not for

therapeutic intervention. There was no evidence that the stem cells had been subjected to any health, safety and quality systems particularly any form of infectious disease screening prior to their use. In the UK, blood and tissue donors are routinely screened for syphilis, hepatitis B, hepatitis C, HIV and human T cell lymphotropic virus (HTLV) as a minimum [19].

The Health Protection Agency (HPA) (now Public Health England) in collaboration with Health Protection Scotland and Public Health Wales conducted an integrated patient notification exercise (lookback) to inform UK residents who had received this stem cell treatment of their potential exposure risk to unscreened stem cells and offer testing for specific infections. The public health response, outcome and lessons learnt from this incident are described.

## Methods

### Management of patient notification exercise

A multi-national incident team composed of public health and scientific experts from the four affected nations was established to manage the incident with respect to notifying patients resident in the UK. Members included representatives from Health Protection Surveillance Centre of the Republic of Ireland, Public Health Wales, Health Protection Scotland, the Health Protection Agency (England), and the National Blood Service. This ensured that a broadly consistent approach to deal with the incident was taken across the UK and Ireland. An individual was present to represent all the communication teams and to liaise with the national press if required.

### Risk assessment

During the incident, investigations were unable to identify the origins of the stem cells used by the GP. The potential infection risks, were therefore identified from current UK guidelines on infectious disease screening, which recommends that blood and tissue donors are routinely screened for syphilis, hepatitis B, hepatitis C, HIV and human T cell lymphotropic virus (HTLV) as a minimum [19].

On the recommendation of the National Health Service Blood and Transplant (NHSBT) the patients were not considered to be at risk of variant Creutzfeldt-Jakob Disease (vCJD). The NHSBT did state however, that the patients in receipt of the stem cells would be classified as transfusion recipients and should be advised that they could not donate blood in the future.

### Identification of exposed patients

A list of names and addresses of patients who had attended the clinic to receive stem cell treatments between February and April 2006, and their GP details (where available), was provided by the GP.

Patients on the list identified as being resident in England and Wales had their GPs and addresses confirmed or identified by cross checking with information held by the NHS Patient Demographic Service. Where the HPA was informed that individuals had died, the HPA undertook a review of death certificates to establish whether or not their cause of death might be associated with stem cell treatment or any infectious disease.

Details of patients resident in Scotland were cross-checked against the register of patients held by the Practitioner Services Division of National Services Scotland (NSS) to confirm details of their GP and to identify any who had died.

Previous diagnosed infection among the patients exposed was established through record linkage with national reports of hepatitis B, hepatitis C and HIV in their respective countries.

### Contacting patients

In England and Wales, letters and blood collecting kits were sent to each patients GP explaining the situation and asking them to forward a letter and information leaflets on blood borne infections to their patient who had been identified as being at risk The letters recommended that patients be tested for HIV, HTLV, syphilis, hepatitis C and hepatitis B. Reminder letters were sent out to the GP if no reply was received. GPs were asked to report whether a patient had since died or moved away. Attempts were made to locate and contact patients who had relocated. Individuals who failed to respond to any of the correspondence were then contacted by their GPs or directly by the investigating agencies and encouraged to take up the offer of testing.

For those patients who were under specialist care, their GP was asked to liaise with the patient's treating specialist and ensure appropriate follow up was undertaken in the appropriate setting.

In England, letters detailing the patients being investigated in each region were also sent to the relevant regional Directors of Public Health.

In Scotland the Consultant in Public Health Medicine (CPHM) of the NHS Board where the patient was resident contacted the patient directly and recommended going to their GP for HIV, HTLV, syphilis, hepatitis C and hepatitis B testing. The CPHM also contacted the patient's GP, providing information on the patient notification exercise, along with the kits to be used to collect blood for screening.

### Infectious disease testing

Serum specimens from patients who agreed to testing were sent to the Virus Reference Laboratory and the Sexually Transmitted Bacteria Reference Laboratory of the HPA.

The UK National Blood Service guidelines on infectious disease screening of donors was used to identify the list of diseases that the patients were potentially exposed to and consequently should be tested. Specimens were tested for antibody to the hepatitis C virus, (anti-HCV), hepatitis B surface antigen (HBsAg), total antibody to the hepatitis B core antigen (anti-HBc total), antibody to the human immunodeficiency virus 1 and 2 (anti-HIV 1 and 2), antibody to human T cell lymphotropic virus types 1 and 2 (anti-HTLV 1 and 2), and syphilis antibodies. If any reactive results were found that were not clearly indicative of infection, the patients were contacted and informed that a further blood specimen was required to confirm the results. Test results were sent to both the patient and their GP.

## Results

A total of 59 individuals from the UK received unscreened stem cells in the IRL between February and April 2006. The majority of these stem cell recipients were female (n=38; 64%). Age at treatment (calculated from when treatments were thought to have ceased) ranged from 2 to 72 years, with a mean of 50 years. The 35 to 54 year old age group had the greatest share of individuals (58%), and 86% of patients were aged 35 or over (Table 1).

| Sex | Age | | | | | Total |
|---|---|---|---|---|---|---|
| | 0-14 years | 15-34 years | 35-54 years | 55-74 years | NK | |
| Female | 1 | 2 | 23 | 10 | 2 | 38 |
| Male | 0 | 0 | 11 | 7 | 2 | 20 |
| NK | 0 | 1 | 0 | 0 | 0 | 1 |
| Total | 1 | 3 | 34 | 17 | 4 | 59 |

**Table 1:** Age and sex breakdown of UK residents exposed to unscreened stem cells in the clinic (including those deceased, n=5).

Cross matching with national hepatitis B, hepatitis C or HIV surveillance data indicated that no patient had previously been diagnosed with a blood borne viral infection. Of the 59 patients identified as being at risk, five patients (8.5%) had died prior to the launch of the investigation. A review of death certification information revealed that none of the deaths were linked to a communicable disease.

Of the remaining 54 patients, one could not be traced (1.7%) and a further eleven individuals (18.6%) declined to be tested or did not respond to follow-up

Forty-two (71.2%) individuals consented to be tested (Table 2). Of these, 40 (95.2%) were confirmed to be negative for hepatitis C, hepatitis B, HIV, HTLV and syphilis. Serum from the remaining two patients showed one had an equivocal result for syphilis and one had reactivity for hepatitis B surface antigen; neither patients provided a second sample for confirmatory testing. Both were confirmed as negative for all other infections (Table 2).

| Outcome of follow-up | Number of individuals | % Individuals exposed |
|---|---|---|
| Tested negative for syphilis/HCV/HBV /HIV/ HTLV | 40 | 74.1 |
| Requested second sample (due to equivocal 1st test results) | 2 | 3.7 |
| Declined testing/did not respond | 11 | 20.4 |
| Could not trace | 1 | 1.9 |
| Exposed to unscreened stem cells | 54 | 100.0 |

**Table 2:** Results of follow-up for patients exposed to unscreened stem cells (excluding those deceased, n=5).

## Discussion

### Main findings of this study

We are not aware of any previous lookback incident which dealt with the public health risk associated with the use of stem cells. This lookback investigation concerned UK resident stem cell tourists who travelled to the IRL to receive unproven stem cell therapies. This paper has summarised the investigation and ensuing patient notification.

In this instance the stem cells used were of unknown origin and had no donor-screening documentation. Forty UK residents who had received the cells were successfully followed up and found to be free of any potentially donor-derived infections. However, two patients were found to have reactivity that warranted follow-up but declined further testing to confirm these results. The investigation could not confirm if any infections were acquired as a result of the administration of these stem cells. If any patients had been confirmed positive for any of the infections investigated it would have been difficult to ascertain whether or not the stem cells were the source due to there being no validated assays for the testing of stored frozen stem cells.

The incident has highlighted a number of issues surrounding the use of these therapies outside of the regulatory environment. Within the issues of safety and quality is the need for the cell origins to be identified prior to use and for the provision of adequate donor cell screening. Central to this investigation was the potential risk of donor-derived infections being transmitted to the stem cell recipients. The quality and traceability of stem cells intended for use in humans is of the utmost importance to ensure recipient safety with respect to transmissible diseases [20,21].

### What is already known on this topic

Stem cell tourism is a growing phenomena and hence, it is not unlikely that similar incidents will occur in the future. Hepatitis B naïve recipients of HBsAg-positive haemopoietic stem cells have been found to acquire infection [22-24] and a high transmission rate of hepatitis C has been observed among previously HCV-uninfected patients receiving HCV RNA-positive stem cell transplants [25]. Although the risks associated with infectious disease acquisition have been documented following receipt of blood products this is not the case with respect to stem cells. However it is believed that cord blood stem cell transplants carry less risk of transmission of blood borne infectious diseases compared with stem cells from the peripheral blood or marrow of related or unrelated donors [26]. To our knowledge there has not been any previous reports of infectious disease transmission via stem cells acquired through medical tourism.

In addition to donor-derived infections there is also a risk of microbial contamination of stem cell lines and isolation, processing and storage of stem cells should be strictly controlled to prevent this [20,21]. Stem cells for use in humans should be routinely screened for such contaminants after processing [19-21]. Reports of complications among stem cell therapy recipients, particularly those involving allogeneic transplants, are well documented irrespective of whether the treatments have been aboveboard [4-6,9,15,27-33].

There are reports of stem cell therapy contributing to non-infectious disease conditions including tumours [4,34]. The only type of malignancy that has been clearly shown to develop as a result of stem cell therapy in humans is donor type leukemia following hematopoietic stem cell transplantation [35]. The difficulties in attributing causal effect of such complications to stem cell therapy provides significant challenges. Although their non-infectious nature poses little public health risk, the impact on the individual's health is very significant. It is pertinent that stem cell treatments conform to the International Society for Stem Cell Research (ISSCR) guidelines [14] in terms of ethical approval, informed consent, regulation and transparency of reporting results.

The internet has undoubtedly aided the rise in stem cell tourism, with 'treatment centres' commonly found by patients online [5,7]. These websites appear to underplay the risks and exaggerate the likelihood of, and potential for, benefit from unproven therapies,

lacking quality evidence to back-up their claimsm [5,7,9]. However, risks are sometimes stated and patients still proceed [10,13]. In many cases, conventional medicine cannot provide a cure for their conditions, and thus patients may perceive any alternatives as worth pursuing in order to maintain hope [6,8,10,12]. This creates difficulties when trying to reduce demand, at a time when treatments are thought to be on the rise as the evidence base increases from rigorously conducted research [8,13]. It has been suggested that regulated, ethically-approved instances of medical innovation for patients with no other viable options should be allowed [8,11,14]. All research should be transparent in the reporting of outcomes in order to prevent future patients facing any unnecessary risk [8,14]. Many of the patients in this investigation were reported to have MS. Although research into how stem cells could be used to treat MS started in the mid-1990s, therapies are still not proven to be safe and effective, and clinical trials are ongoing [17,28,32].

Further still, the patients' stage and type of MS can affect the outcome of treatment, with malignant, relapsing patients without severe disability being most likely to benefit, and late-stage progressive patients least likely to benefit [28-30,32,36,37]. This poses a dilemma as there is likely a bias towards the most advanced-stage patients wanting to pursue stem cell therapies, be that inside or outside of the regulatory environment. That five patients in this investigation had died since their treatment may suggest that this is the case. Vulnerable patients often pay to buy and receive these unproven therapies [5-7,13] as patients did in this incident, for which they may not receive the same standard of care and follow-up as those in ethically approved and regulated situations.

### What this study adds

There is no conclusive evidence of infectious disease transmission in this lookback investigation, however therapies involving unscreened stem cells do carry this potential risk. There is a duty of care to follow-up any patients known to have received unscreened stem cells and stem cells which cannot be certified suitable for clinical use. It is of the utmost public health importance to question the source of cells used in such treatments when unregulated or unauthorised practices come to light. Patients in receipt of stem cells are classified as transfusion recipients and are currently advised that they should not donate blood.

### Limitations of this study

The main limitation of the study was the failure to engage all patients with the lookback exercise and follow-up process. However, it is the patient's right to decline testing in such a public health investigation. There is a clear misalignment of public/patient understanding and scientific findings in this complex area of stem cell research.

## Conclusions

The involvement of patient groups [5,6,13] and the launch of the ISSCR patient website [38] are key to increasing patient understanding and reducing demand for unregulated stem cell therapies. During this investigation the Multiple Sclerosis Society posted a warning on their website regarding the experimental nature of stem cell therapies in treating MS and called on patients to think carefully about the risks involved. The media also has an important role to play and must be cautious in translating scientific findings to the public [6]. Individuals considering treatments should ensure they are fully informed and consult their GP or consultant. Dialogue with patients through patient groups and the ISSCR patient website may be crucial to limiting demand for stem cell tourism as research into their therapeutic use advances.

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