Cross border reproductive care - the EUTCD perspective

We live in a world with no medical borders. An ever-increasing number of patients with infertility or desiring a family through ART, in the circumstances of physiological impossibility of conceiving or carrying a pregnancy, are seeking treatment outside their country of residence. Furthermore, couples that want to avoid the transmission of an inheritable condition to their offspring are willing to travel to countries where techniques like Pre-Implantation Genetic Diagnosis (PGD) are practiced.

The European Society for Human Reproduction and Embryology (ESHRE) has studied this phenomenon of Cross Border Reproductive Care (CBRC) and established a ESHRE CBRC Task Force which proposed guidelines on the delivery of care in the circumstances of CRBC.

The present paper will look at the challenges of implementing the European Directives in the circumstances of CBRC. I will specifically deal with a short summary of the legal requirements, limited data on CBRC and relevant challenges for the parties involved, namely the patients, the country of residence and the “child to be”.

The legal requirements

The quality and safety of reproductive laboratory activity has been addressed by the EU Directives 2004/23/EC, 2006/ 17/EC and 2006/86/EC as early as 10 years ago1,2,3. The transposition into law, in each European country, ensures that individual patient interests and public health are safeguarded at pan-European level.
The 2004/23/EC (Mother) Directive deals with standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, as pertinent to the field of Assisted Reproduction. The 2006/ 17/EC (Technical 1) Directive addresses the technical requirements for the donation, procurement and testing of human tissues and cells while the 2006/86/EC (Technical 2) Directive details traceability requirements, notification of serious adverse reaction/ events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

Each European country was requested to transpose the Directive into national law and establish a national Competent Authority (CA) to supervise the implementation of such national laws. Among the duties of the CA is the requirement to inspect and license all ART laboratories in the country. Specifically, all Assisted Reproductive Technology (ART) units must be authorized, accredited and have efficient quality systems run by a Quality Manager.

From a clinical perspective the requirements refer to:

a. risk reduction (serology testing of all patients embarking on ART where processing of a reproductive sample, i.e. sperm, oocytes, embryos, including frozen tissues and cell, is to take place; evidence of certified training and training re-validation on regular basis);

b. identification of risk (compulsory serious adverse events and reactions (SARE) reporting) and long-term follow-up (confidentiality and data storage for 30 years).

At laboratory level clear stipulations cover:

a. processing (air quality, microbial and particle monitoring),

b. storage of reproductive material (continuously monitored, infectious risk segregated),

c. traceability (from donor to recipient),

d. coding (unique identifier code for all reproductive material that is exported to another country) and

e. compulsory reporting of SARE in the laboratory sphere.
Cross Border Reproductive Care (CRBC)

CRBC or the process of obtaining or providing reproductive treatment outside patient’s home country has been extensively studied previously\(^4\). There is a double flow across European and world borders at present (Figure 1).

**Figure 1.** Cross-border movement of patients and reproductive material.

It is crucial to acknowledge that both patients and reproductive material regularly transit inter-country borders. Only the later are monitored and regulated part of the implementation of EUTC national laws and under the supervision of national Competent Authorities.

Research data from Europe\(^4\) suggest that 6% (1 in 16) ART treatments in Europe are performed outside the country of residence. The authors quote up to 30,000 cycles yearly, performed for up to 20,000 patients. In the US, the Centre for Disease Control reported and incidence of 4% (6,000 cycles) in 2008\(^5\).

**Areas of risk during CBRC**

During the provision of medical care for couples seeking ART therapy each step of the process carries risks (Table 1).
Table 1. Areas of risk in CRBC.

<table>
<thead>
<tr>
<th>Selection</th>
<th>Processing</th>
<th>Distribution</th>
<th>Storage</th>
<th>Clinical</th>
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</thead>
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<tr>
<td>Medical</td>
<td>Lab infection</td>
<td>Mix-up</td>
<td>Loss of RM</td>
<td>Severe reaction</td>
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<tr>
<td>Genetic</td>
<td>Infectious</td>
<td>Material</td>
<td>Tank failure</td>
<td>reaction</td>
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<tr>
<td>Infectious</td>
<td>Culture media</td>
<td>Loss of</td>
<td></td>
<td>OHSS</td>
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<tr>
<td>Misdiagnosis</td>
<td></td>
<td>material</td>
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**Selection**

The patient selection process involves responsibility in selecting right donors, free of genetic diseases like cystic fibrosis (CF) or infectious conditions like Hepatitis or HIV that can be transmitted to the recipient or the offspring (CF). Similarly, practitioners should ensure that patients themselves are suitable for therapy and pregnancy. For example, in women with Turner Syndrome (45,XO), co-arctation of the aorta, a congenital malformation well described in this group exposes both the pregnant woman and her baby to a major risk (50% likelihood), namely maternal death during pregnancy. Practitioners have a duty to inform all such patients, prior to egg donation, of the risks ahead and even advise them against a pregnancy in the circumstances of above evidence.

**Processing**

The processing of sperm and eggs in the ART laboratory falls under the European Directives. Even with the best quality systems in place errors during the fertilization, incubation (storage), assessment and release of gametes or embryos can occur. Some of the errors can have significant implications.

Infection occurring in the culture dish (from one of the partners) as the semen is not a guaranteed sterile environment, neither is the vagina. Vaginal bacteria can
contaminate the oocyte collection needle and such infection can be evident in the culture media after extensive culture. Any alteration in culture media parameters due to either faulty production or transport and storage can have a dramatic impact upon the development of embryos in vitro, in worse scenarios resulting in total loss of embryos.

Misdiagnosis of normality in an affected embryo after pre-implantation genetic diagnosis (PGD) is particularly unfortunate as couples avail of such services in order to specifically find an unaffected embryo. Usually, this is not related to the test performance but to the erroneous allocation of a result to a specific embryo.

Distribution

The release of embryos for transfer can result in undesired complications for the patients.

Mix-up of gametes or embryos is a well-described complication of ART. For couples embarking in CBRC is has devastating consequences, particularly as many have attended for specific purpose (donor eggs, sperm or embryos; PGD). Loss of embryos at time of transfer is a theoretical occurrence. Culture dish dropping with the consequent loss of embryos can occur in practice yet, no cases have been published to date.

Storage

Tank failure is a recognized clinical occurrence and unless full remote monitoring is in place will result in total loss of reproductive material. Cross-infection can occur in the circumstances of poor sealement of storage vessels and use of non-high security straws for cryopreservation. Sample segregation (separate storage for couples where a partner is seropositive) and the use of high security straws should eliminate this risk.

Reproductive material samples can be lost as consequence of storage vessel breakage when the material is release in the liquid or vapour nitrogen environment. Appropriate training, handling of stored canes only when required and following procedures carefully reduce such risks to a minimum.

Clinical

Severe reaction to recommended medication used is rare but potentially severely damaging. Of interest is the use of medication with scientifically unproven
benefits which could potentially expose patients to unnecessary risks (steroid or anticoagulant use). Any oocyte collection surgical procedure exposes females to the risks of injury to pelvic organs like bowel or blood vessels, which may present days after the oocyte collection operation performed abroad. Ovarian hyperstimulation syndrome, a potentially lethal complication of ovarian stimulation occurs in 1% of all treatments. The patient attending for ART abroad could present as late as 7-9 days afterwards to the services in the country of residence. Severe dehydration, vomiting, renal and respiratory failure with death are well described in the literature. Management is ambulatory in mild cases and requiring admission with intensive care is severe. From a stimulation and procurement perspective not all clinics follow up their patients after treatment or after a pregnancy establishes. It is notoriously difficult to obtain post treatment data. As such events like OHSS will not be always known to the treating IVF centre and thus not reported.

Such serious adverse events and reactions occurring during or after treatments abroad require compulsory reporting to national CA as specified by the recommendations made in the SOHO V&S EU Project 6 (Figure 2).

**Figure 2.** Recommendations on occurrence of SARE in CRBC.

<table>
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<th>CA’s should encourage health professionals to report SARE even when it is established to be related to ART CBRC.</th>
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<td>In the case of CRBC, the CA receiving the SARE notification should inform the other CA’s concerned without any delay.</td>
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<tr>
<td>CA’s should encourage Tissue Establishments (TE’s) to promote information about any adverse outcomes.</td>
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Furthermore, the Guidance on Vigilance provides all units and practitioners with examples of risks and risk assessment tools to be used in practice.

Nevertheless, the implementation of ART vigilance raises some very specific challenges in that practitioners and clinics that report could become a target for the
press and suffer loss of business despite doing the “right thing”. The issue is not what to report but how to encourage clinics to report SARE while maintaining patient confidence and not creating unnecessary anxiety among patients?

The couples

The main services accessed by couples seeking ART abroad are donor gametes or embryos, surrogacy, PGD, gender selection and cheaper IVF/ICSI treatments. While English is spoken widely it is envisaged that language barriers will exist for couples availing of CBRC. Any decision to proceed with therapy is based upon a good understanding of procedures, risks and potential complications. While ART services routinely present extensive or less extensive medical information to their patients, if a language barrier exists it is possible that couples might not be making an informed choice prior to pursuing treatment.

From a medical perspective, patients must be aware that the likelihood of receiving safe treatment and conceiving varies according to many aspects of care. Furthermore, if medical complications have occurred, the lack of medical information, particularly if an acute event that precludes patient cooperation, makes patient management far more difficult. A non-exhaustive list of important “good medical practice” standards expected from ART units\(^6\) are detailed in Table 2.

Table 2. Standards of care expected in all European ART units according to EU law.

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<td>Trained and accredited medical, nursing, embryology staff</td>
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<td>Fully monitored laboratory equipment</td>
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<td>Appropriate laboratory air quality monitoring</td>
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<tr>
<td>Quality systems</td>
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<tr>
<td>Segregated tissue storage, fully monitored</td>
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<tr>
<td>Written procedures followed for all cases</td>
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<tr>
<td>Compulsory testing of donors</td>
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<td>Compulsory testing of surrogates</td>
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From a legal perspective different countries have different stipulation in relation to the provision of ART and some have no ART law at all. In consequence, it is very unlikely that any recourse to legal support in the country of residence, in the circumstances of a medically culpable service abroad, will be available.
The country of residence

The impact on the medical and legal system of the residence country is not negligible.

Cross border reproductive care (CBRC), or the movement of patients within the EU member states or to neighboring non-EU countries, seeking ART treatment outside their country of residence has been in existence for many years now. The ESHRE CBRC Task Force has published Guidelines of good practice: ESHRE's Guide to Cross-border Reproductive Care\textsuperscript{8}.

The services in the country of origin will normally take the burden of complication like care for multiple pregnancies, particularly in high-risk patients, complications immediate after therapy (OHSS) and the ability to allocate a true legal status for the children born. Also, traceability remains the significant challenge where cross border care has been provided as many non-EU countries have no ART laws and no data collection on the outcomes of ART therapy. For example, the reality about genetic diseases and donor reproduction is that neither the donors nor the parents of a child can be forced to report a genetic disease. Adults that develop genetic diseases after donation might not want to return to the Donor Recruitment centre to make them aware, while the reporting of a birth of a child with a genetic disease can happen only if the parents inform the centre. As such, any reporting of genetic disease after donation is voluntary at the donor and recipient end. To encourage reporting, EU financial vehicles need to be put in place to cover the costs associated with such diagnoses, legal challenges and long term care of both the donor and the diagnosed child.

As regards the ART practitioners in a country where CBRC, where does their responsibility start and finish? The American Society for Reproductive Medicine (ASRM) guideline on Cross Border Reproductive Care\textsuperscript{9} raised a few important questions: What duties does the physician have to inform the patient about the opportunities for care and risks and benefits specific to treatments abroad? Even more important what duty, responsibility to care for a patient that returns to the country of origin, particularly in the circumstances of a poor outcome and no treatment details or medical records, the physician has?

As regards Europe, it is unrealistic to expect that obstetricians working outside the ART units, and thus not falling under the umbrella of the EUTC Directive, will
report any SARE to the CA. There is no obligation upon such practitioners to report any events and furthermore they have a duty of patient confidentiality, which will take precedence. From previous experience with implementing the EUTCD this vigilance recommendation is unrealistic and will not easily be implemented in the EU countries. Ideally, a close interaction between the ART practitioner providing the treatment and the practitioner that does the follow up of the CBRC patient (once it returns to its country of origin) should be encouraged and nourished. Only then the patient will have a smooth transition of care from provider to follow up physician and all adverse events easily identified, reported and followed up.

The child to be

The future child’s wellbeing and ability to know their origins, genetic or social as well as their upbringing is a topic that does not currently receive enough attention.

While the issue of donor anonymity has preoccupied both patients and regulators for a long time, country specific legislation varies across Europe and the issue of pan-European identification of donors is, at least at present, utopic.

If a patient receives treatment in an European country where the donor anonymity is guaranteed there is no legal obligation for the provider of the reproductive material sample or the treatment centre to release any donor related information to a third party. Specific cases, where the release of information is necessary in the interest of reducing future harm (i.e. transmission should be explored through the Competent Authorities rapid alerts systems in place in all European countries. Yet, should all parents of children born from donor treatments be forced by law to discuss the mode of conception and the genetic origins with their child?

What about children that have been born abroad using surrogacy and which have no legal rights in the country where their family resides? In the majority of European countries surrogacy is not practiced. Couples are forced to pursue such therapy abroad or indeed on a different continent. The legal paperwork on return home is a challenge and will expose their children to the risk of no birth certificate or national identity and significant inheritance challenges.

Many centers offer the promise of “pregnancy” at your desired age” by promoting egg freezing, social or for donation. The main concerns are related to poor patient information, false sense that pregnancy at advanced maternal age is a
desirable, safe and realistic family option and the ethical issue of creating reproductive banks for convenience only. A significant difference exist between freezing where a medical indication exists (family history of premature ovarian failure, severe medical conditions that affect ovarian function or where adjuvant therapy like chemo or radio therapy is required) and social freezing where an individuals desire to delay conception is the main reason for the intervention. Yet, it appears that, particularly the latter, is fast moving, away from the practice of medicine and into the convenience or social fad. One can envisage that children born from socially frozen eggs will be exposed to unnecessary risks related to pregnancy specific risks at advanced maternal age. Furthermore, such born children might find themselves orphans, before reaching maturity with all the associated social and psychological consequences attached to such a life-altering scenario. Last but not least, important issues like who owns the reproductive material, who is allowed to use it, can it be inherited or passed on to next generations are awaiting societal, legal and medical answers. Of particular concern is the potential patient exploitation through storage fees for a long period of time.

References