Venturing Into Alternative Therapies: Stem Cell Research in the Kingdom of Bahrain

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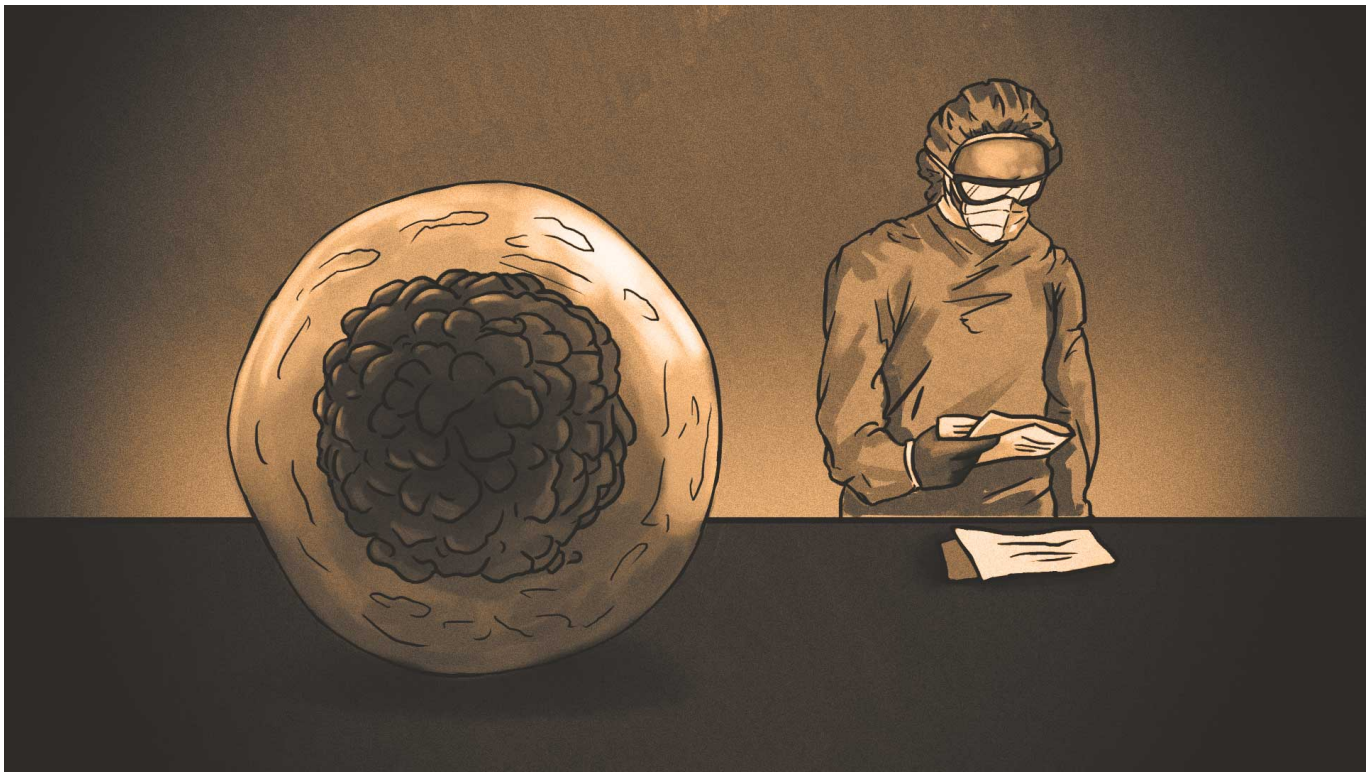

*This illustration is inspired by the original photo of **Mahatma Gandhi Spinning** by Margaret Bourke-White.*

In the past decade, multiple nations in the MENA region have increased their focus on enhancing scientific capabilities in order to tap into the prospects and benefits associated with stem-cell research. The prospect of cell proliferation has driven various regulators to establish suitable guidelines to govern research and development in the field of stem cell research. This article provides a high-level overview of some of the key legislative developments taking place in Bahrain in the field of stem cell research.

In 2019, the National health Regulatory Authority of Bahrain ('**NHRA**') surfaced a comprehensive guideline on conducting clinical trials in Bahrain, encompassing special provisions stem cell research – Clinical Trials by Using Stem Cells Regulations (v.1 2019) ('**CTSCR**'). Licensed healthcare facilities willing to engage in clinical trials for the purposes of exploring novel therapies in the sphere of stem cell science are required to adhere to stringent conditions prior to commencing such activities. In this regard, the CTSCR were implemeted to tackle clinical research trials of human non-embryonic autologous and allogenic (limited to hematopoietic) based stem cell research.

Article 83 of CTSCR stipulates that autologous stem cells procured for clinical trials may be obtained from the following sources:

1. Cord blood stem cells collected from umbilical cord after the delivered of a healthy newborn;
2. The placenta, its membranes and amniotic fluid obtain from healthy human tissue; and
3. Different human tissues after birth, which may include somatic stem cells for the production of Induced Pluripotent Stem Cells.

Conversely, the CTSCR prohibits the use of embryonic stem cells, hybrids, and chimeric somatic stem cells produced from nonhuman cells, stem cells obtained from somatic cell nuclear transfer to an unfertilized ovary, in addition to the creation of human embryonic stem cell lines from blastocysts.

To date, the NHRA only authorises clinical trials conducted in the following phases:

1. Phase II: the testing of drugs on patients to assess efficacy and side effects. This involves 100-300 participants and usually lasts up to two years;
2. Phase III: the testing of drugs on patients to assess efficacy, effectiveness, and safety. This involves 300-3,000 participants and usually lasts up to one to four years;
3. Phase VI: the post-marketing surveillance. This involves thousands of participants and usually lasts up to 1+ years.

As a baseline, biotechnology, and pharmaceutical entities, clinical research organisations, and licensed medical facilities that demonstrate proof of adequate training in stem cells science or regenerative medicine and hold the following certifications are permitted to engage in conducting clinical trials in Bahrain:

1. Current Good Manufacturing Practices;
2. Good Tissue Practices;
3. Good Laboratory Practices; and
4. Good Clinical Practice (ICH-GCP R2, 2016) ('**GCP'**).

Moreover, an emphasis has been placed on licensed medical institutions to appoint an independent research ethics committee ('**IREC**') responsible for the review, approval, monitoring, and reporting of the progress of clinical trials taking place at their respective institutions, in line with Version 1.0 of the NHRA's Standards & Requirements for Independent Research Ethics Committee Involved in Clinical Trials in the Kingdom of Bahrain ('**IREC Guidelines**').

The IREC Guidelines adhere to the ethical principles of autonomy, beneficence, non-maleficence, and justice and were drafted in line with international standards adopted by the World Health Organization ('**WHO**') and International Conference of Technical Requirements for the Registration of Pharmaceuticals and for Human Use. As eluded to in Standard (3) of the IREC Guidelines, the membership of an IREC shall consist of no less than five members, satisfying the following minimum requirements:

1. At least two persons with experience and expertise in the design and conduct of intervention studies;
2. At least one member whose primary area of interest is in a nonscientific area; and
3. At least one member who is independent (non-affiliated) of the institution/trial site.

In this regard, a member falling under category (c) of the IREC structure is expected to not be a health professional nor exposed to any conflict of interest by way of kinship with a member of the research team or potentially holding a financial stake in the research project.

Importation of Stem Cells

The importation of any type of stem cells used in clinical trials is subject to authorisation by the NHRA. Additionally, applicants are required to be in possession of the following documents at all times when importing stem cells to Bahrain:

1. Quality certificate documenting the viability and pre-screening for infection/ genetic mutation of the imported cells at the time of customs clearance;
2. Proper documentation of the shipping and storage conditions. In this regard, note that the NHRA requires somatic stem cells to adhere to local data protection law (i.e. Law (30) of 2018 on Personal Data Protection ('**PDPL**')). However, in the event that such trials are conducted in affiliation with a European academic institution or medical centre, the NHRA would accept samples adhering to the General Data Protection Regulation); and
3. Records of pre-implantation/injection analysis of stem cells to be administered to research subjects.

Insuring Safety

The NHRA mandates applicants to subscribe to a clinical trial insurance package to covering potential fatalities or injuries sustained amid clinical trial procedures. Equally, participating clinical researchers are required to obtain malpractice insurance providing coverage during the trial period. The aforementioned breadth of coverage must extend to injuries resulting from acts of omissions, errors, or gross negligence. However, it is worth noting that in the event of an injury emanating from a clinical trial product or protocol procedure, as set out by the institution or entity undertaking the clinical trial, any payable damages shall rest on the insurance policy procured by the institution or entity. An additional layer of coverage addressing corporate liability must be factored in by institutions and entities sponsoring stem cell research activities.

In addition to maintaining watertight coverage against undesired outcomes, applicants are required to present several safeguards in the form of proof of clinical trial registration in any WHO-approved clinical trial registries, comprehensive study rationale setting out the potential risks and benefits, primary and secondary objectives, study design, and eligibility criteria of the prospective cohort.

In all events, an entity sponsoring a clinical trial, institution, or healthcare facilities managers, principal researchers, or members of the IREC are mandated to report any serious deviations, serious and continuous non-compliance, fraud, or misconduct once it has come to their attention. Article 69 of CTSCR authorises both the NHRA and IREC to take all necessary measures (including the right to suspend research privileges) in the event of repeat deviations, continuous non-compliance or fraud and research misconduct.

The following definitions stipulate the scope of the abovementioned transgressions:

- **Protocol Deviation**: Any departure from the approved protocol, associated trial documents, or any other information relating to the conduct of the trial that does not result in harm to the trial participants and does not significantly affect the study outcomes;
- **Protocol Violation**: Any departure from the approved protocol, associated trial documents, or any other information relating to the conduct of the study thatmay affect the safety of trial participants or the study outcomes;
- **Non-compliance**: Failure to comply with the protocol, NHRA regulations, IREC, or institutional policies and standard operating procedures, GCP and/or other applicable regulatory requirements:

1. Minor non-compliance: Non-compliance involving isolated incidents or minor or technical violations that

result from an unintentional mistake, an oversight or a misunderstanding, or failure to follow operational procedures, protocol, or good clinical practice that do not pose risk to subjects or violate the research subject's rights and welfare.

2. Serious Non-compliance is composed of either one or more transgressions from the following violations:
   - exposing research participants to a significant risk of substantive harm;
   - compromising the privacy and confidentiality of research participants;
   - causing damage to the scientific integrity of the research data that has been collected;
   - engaging in willful or knowing noncompliance; and/or
   - impacting ethical principles adversely.

Consent, Storage, Disposal

Healthcare institutions and research sponsors are required to obtain donor and recipient consent through adhering to the recommendations set out in the Declaration of Helsinki – the conventional ethical principles surrounding human experimentation and research using human biological material. Where a stem cell donor is below the age of 21 years, a legal guardian would be required to provide consent on behalf of the trial subject in his capacity as his/her legal proxy. The directives appearing on the CTSTR impose the provision of the following information – without prejudice to the rights of data owners provided for in the PDPL – in donor and recipient consent forms:

1. risk factors including biological and procedural risks;
2. voluntary nature of participation and right to withdraw consent at any stage of the clinical trial; and
3. anonymisation and encryption of the donor's personal data.

Moreover, the storage of stem cells shall be performed in compliance with current Good Laboratory Practices and Good Tissue Practices. Once stored, stem cells shall undergo screening for genetic and infectious diseases. In the event of disposal, entities and institutions are required to adhere to biological waste management best practices.

Conclusion

With a broad emphasis placed on harmonising local stem cell research guidelines with international best practices, the Kingdom of Bahrain demonstrates a promising playing field in cutting edge clinical research. Auspicious moves have been observed from the Kingdom's clinical training institutions with the unveiling of state-of-the-art clinical trial centers at the King Hamad University Hospital and Arabian Gulf University Clinical Research Centre. As for the latter institution, a recent postgraduate course in regenerative medicine has been launched in 2020, in a significant move aimed towards investing in evidence-based biologic medicine. Consequently, hospitals, research institutions, and sponsoring entities must be mindful of the regulatory prerequisites, privacy considerations, and adherence to all the relevant international conventions and best practices before opting into stem cell clinical trials in Bahrain.

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