

D4.2: Guidelines for Promoting Quality and Safety of hPSC-based Medicines and Cell Therapy Products

The extended version of this deliverable is under submission to be published as an open access full paper.

Working Group 4: Safety and Regulation

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Disclaimer: Preparation of the first draft of this document was assisted by AI language tools (Perplexity Pro and Claude). All content has been critically reviewed, corrected, and substantially revised by WG4 members. All references have been independently verified against primary sources. Responsibility for the content rests with the authors and the HAPLO-iPS Action.

Summary

This report constitutes Deliverable D4.2 of the HAPLO-iPS COST Action (CA21151), produced by Working Group 4 (Safety and Regulation). This deliverable combines a review of existing regulations with a stakeholder-informed analysis of regulatory gaps specific to HLA-homozygous iPSC haplobanking.

The review covers nine major guideline families: the WHO 2023 regulatory framework; the EU Directives and EMA guidelines on human cell-based and stem cell-based medicinal products; the FDA biologics and cellular/gene therapy framework; PMDA/MHLW technical guidance for processed-cell and regenerative medicine products; ICH horizontal quality standards (Q5A(R2), Q5D, Q6B, Q9(R1), Q13); and the professional and registry standards of ISSCR, hPSCreg, ISCBI, ISCI, and ISO.

The core regulatory question for HAPLO-iPS is not merely which guidelines exist, but which combination of requirements governs the path from HLA-typed cord blood donation through reprogramming, cell banking, clinical-grade manufacturing, and ultimately to allogeneic transplantation of hiPSC-derived cell products. The findings of this report are therefore intentionally framed to serve all seven working groups, with targeted consortium recommendations.

Key findings are: (a) no single globally applicable hPSC-specific guideline exists, and the strongest current approach remains a composite of EMA lifecycle structure, FDA modular risk-based guidance, PMDA cell-product specificity, ICH horizontal quality standards (which provide the cross-jurisdictional CMC architecture underpinning all three regional frameworks), and ISSCR translational standards; (b) assay standardisation, especially for residual pluripotency, genomic stability, and tumorigenicity, remains the most critical unresolved gap; (c) the allogeneic, HLA-haploidentical context of HAPLO-iPS raises specific regulatory needs around donor eligibility, immunogenicity assessment, and HLA banking that current guidelines address only partially. The HAPLO-iPS initiative is additionally positioned to address an emerging regulatory challenge not yet formally recognized in existing guidance: the standardization of HLA-homozygous hiPSC haplobanking as a clinical-grade source-material framework integrating population genetics, donor traceability, immunological compatibility, and long-term recipient monitoring.

The consortium-specific recommendations call for active alignment of the registry, SOP, characterisation, and safety outputs of WG1–WG7 with regulatory expectations set out in this document.

Recommendations for the HAPLO-iPS Consortium

The following recommendations are addressed to the HAPLO-iPS COST Action (CA21151) working groups. They are designed to align the Action's scientific deliverables with regulatory expectations and to position the consortium's outputs as primary inputs to the regulatory and standards gaps identified above.

- **WG1 (Sample Selection):** Develop and publish the HLA-typing and cord blood eligibility criteria as a consortium white paper that can serve as a reference for regulators formulating haploidentical donor standards. Documentation should include population-level haplotype frequency modelling, ethnic representation data, minimum cord blood unit quality parameters, and traceability chain from donor to master cell bank.
- **WG2 (hiPSC Production):** The SOP on hiPSC generation from haplo-selected cord blood samples should explicitly address ICH Q5D cell banking requirements, viral safety testing per ICH Q5A(R2), genomic integrity surveillance methods, and reprogramming-method-specific safety considerations. The SOP should be structured to support direct citation in a future IND/CTA filing.
- **WG3 (Quality Control, Biobanking and Registration):** Align the HAPLO-iPS registry data model with ISO 24603:2022 and hPSCreg registration criteria, and extend it to capture HLA allele-group data, reprogramming history, passage number at clinical-grade banking, and viral safety testing status. Develop and publish the registry access and governance model as a potential template for national haploidentical iPSC registries. The registry architecture should additionally support future integration of population-level HLA coverage models, immunogenicity metadata, and long-term clinical follow-up datasets.
- **WG4 (Safety and Regulation):** Develop an action-level consensus guidance document on: (a) minimum genomic stability testing requirements for clinical-grade haploidentical hiPSC lines, specifying methods and timepoints; (b) tumorigenicity testing strategy adapted from PMDA 2016 for cord blood-derived iPSC products; and (c) immunogenicity assay design for allogeneic hiPSC-derived products in HLA-haploidentical recipients. Submit these documents to EMA CAT, FDA Office of Therapeutic Products (OTP), and PMDA for scientific opinion under pre-submission consultation procedures. WG4 could additionally position HAPLO-iPS as a future reference framework for the regulatory qualification of HLA-homozygous hiPSC haplobanks through coordinated interaction with EMA CAT, FDA OTP, ISSCR, hPSCreg, and ISO working groups. Develop a consensus in coordination with regulators on the process to establish that a change in manufacturing cell line delivers an equivalent product.
- **WG5 (Management, Data Handling and Ethics):** Ensure that donor consent forms for cord blood collection include explicit consent language for: commercial-scale hiPSC production; registration in public databases; transfer of donor consent (when infant donors reach adulthood), limits to right to withdraw, use in allogeneic transplantation; future HLA-matched recipient identification; and potential genomic data sharing with regulatory agencies. The consent framework should comply with GDPR Regulation (EU) 2016/679 and be harmonised across HAPLO-iPS partner countries as much as current national legislations allow.
- **WG6 (Training and Dissemination):** Develop and deliver a regulatory science training module for Action members and external stakeholders covering the composite regulatory framework for hiPSC-derived allogeneic therapies. Engage EMA, FDA, and PMDA representatives as external speakers at consortium workshops to build mutual familiarity between the consortium's scientific outputs and regulatory expectations.
- **WG7 (Clinical Application):** Design transplantation protocols for hiPSC-derivative therapies to include, from the outset, an LTFU component consistent with FDA's 2020 LTFU guidance and EMA's

ATMP pharmacovigilance expectations. Identify a clinical partner or contract research organisation that can operate a HAPLO-IPS clinical registry capable of capturing minimum 5-year post-transplant follow-up data across multiple sites and jurisdictions. Clinical protocols should incorporate predefined immune-monitoring strategies including donor-specific antibody assessment, allo-sensitisation surveillance, and longitudinal immune profiling and a strategic approach to setting dose and potency assays.

References (to be explained in details in the full paper)

- Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO). Donation of starting material for cell-based advanced therapies: a SaBTO review. London: Department of Health; 2014.
- Allison TF, Andrews PA, Avior Y, et al., on behalf of the International Stem Cell Initiative (2018) Assessment of established techniques to determine developmental and malignant potential of human pluripotent stem cells. *Nature Communications*, 9. 1925. <https://doi.org/10.1038/s41467-018-04011-3>
- Andrews PW, Baker D, Benvenisty N, Miranda B, Bruce K, Brüstle O, Choi M, Choi YM, Crook JM, de Sousa PA, Dvorak P, Freund C, Firpo M, Furue MK, Gokhale P, Ha HY, Han E, Haupt S, Healy L, Hei DJ, Hovatta O, Hunt C, Hwang SM, Inamdar MS, Isasi RM, Jaconi M, Jekerle V, Kamthorn P, Kibbey MC, Knezevic I, Knowles BB, Koo SK, Laabi Y, Leopoldo L, Liu P, Lomax GP, Loring JF, Ludwig TE, Montgomery K, Mummery C, Nagy A, Nakamura Y, Nakatsuji N, Oh S, Oh SK, Otonkoski T, Pera M, Peschanski M, Pranke P, Rajala KM, Rao M, Ruttachuk R, Reubinoff B, Ricco L, Rooke H, Sipp D, Stacey GN, Suemori H, Takahashi TA, Takada K, Talib S, Tannenbaum S, Yuan BZ, Zeng F, Zhou Q. (2015) Points to consider in the development of seed stocks of pluripotent stem cells for clinical applications: International Stem Cell Banking Initiative (ISCB). *Regen Med*. 10(2 Suppl):1-44. doi: 10.2217/rme.14.93. PMID: 25675265
- Andrews PW, Ivana Barbaric, Nissim Benvenisty, Jonathan S. Draper, Tenneille Ludwig, Florian T. Merkle, Yoji Sato, Claudia Spits, Glyn N. Stacey, Haoyi Wang, Martin F. Pera (2022) The consequences of recurrent genetic and epigenetic variants in human pluripotent stem cells, *Cell Stem Cell*, 29 (12) 1624-1636, <https://doi.org/10.1016/j.stem.2022.11.006>.
- Azuma, K., et al. (2023). Country-specific regulation and international standardization for stem cell-derived products. *Regenerative Therapy*, 24, 92–102. <https://pmc.ncbi.nlm.nih.gov/articles/PMC10444560/> [Note: full author list should be verified against the published article.]
- Brouwers, M. C., Kho, M. E., Browman, G. P., Burgers, J. S., Cluzeau, F., Feder, G., Fervers, B., Graham, I. D., Grimshaw, J., Hanna, S. E., Littlejohns, P., Makarski, J., & Zitzelsberger, L. (2010). AGREE II: Advancing guideline development, reporting and evaluation in health care. *Canadian Medical Association Journal*, 182(18), E839–E842. <https://doi.org/10.1503/cmaj.090449>
- Creasey AA, Stacey GN Bharti K, Sato Y, Lubiniecki A. (2019) A strategic road map to filing a Biologics License Application for a pluripotent stem cell derived therapeutic product *Biologicals*, 59; 68-67. DOI: 10.1016/j.biologics.2019.03.007
- De Sousa, P. A., Steeg, R., Wachowicz, K., Zeng, X., Li, J., Cabral, J. M. S., Silva, C. L., & Vallier, L. (2020). Improving the safety of human pluripotent stem cell therapies. *Nature Communications*, 11, Article 2498. <https://doi.org/10.1038/s41467-020-16455-7>
- European Medicines Agency. (2008, May 30). Guideline on human cell-based medicinal products (EMA/CHMP/410869/2006). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-human-cell-based-medicinal-products_en.pdf
- European Medicines Agency. (2011, February 2). Stem cell-based medicinal products: Scientific guideline. <https://www.ema.europa.eu/en/stem-cell-based-medicinal-products-scientific-guideline>
- European Medicines Agency. (2016, updated). PRIME: Priority medicines scheme. <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/prime-priority-medicines>

- European Parliament and Council of the European Union. (2007). Regulation (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32007R1394>
- Food and Drug Administration. (2020a, July 20). Regulatory considerations for human cells, tissues, and cellular and tissue-based products: Minimal manipulation and homologous use. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products>
- Food and Drug Administration. (2020b). Long term follow-up after administration of human gene therapy products: Guidance for industry. <https://www.fda.gov/media/113768/download>
- Food and Drug Administration. (2021b). Expedited programs for regenerative medicine therapies for serious conditions: Guidance for industry. <https://www.fda.gov/media/120267/download>
- Food and Drug Administration. (Accessed May 2026a). Cellular & gene therapy guidances [CBER guidance catalogue]. <https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances>
- Food and Drug Administration. (Accessed January 2026b). Cellular & gene therapy products [CBER product overview]. <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products>
- Hägg A, Wood R, Abberton K, Abranches E, Alvarez-Palomo B, Baptista R, Barbosa RAQ, Barry J, Carvalho AB, Bennaceur Griscelli A, Campos de Carvalho AC, Chaker D, Chang H, Choi HY, Codinach M, Corbella BA, Cowan S, Dickerson SJ, Elwood N, Fan X, Feyeux M, Forrester M, Gaffney A, Guilbert SM, Ha HY, Hikichi T, Hirst AJ, Hunter AL, Jamieson LG, Judson RN, Kanemura Y, Kasai-Brunswick TH, Kim JH, Kim H, Kintali M, Krishnan S, Kuebler B, Lau CY, Li W, Mack A, MacLeod MR, Madrid M, Mamiya H, Manache-Alberici L, Mărginean D, Mentre O, Mochizuki A, Morgan SL, Mountford J, Munir H, Ng SHS, Ogawa H, Oh S, Ohara H, Oono K, Park N, Pereira LV, Pereira da Silva Bezerra I, Podovei AR, Querol S, Raje J, Raya A, Sakamoto S, Sarafian R, Schmit K, Selvitella S, Singh G, Smart MJK, Song J, Stacey G, Sullivan S, Sumida M, Terrenoire C, Tian P, Uhlin E, Vaquero JMA, Veiga A, Wang JWV, Warre-Cornish K, Wood J, Yamamoto A, Zhang G, Turner M, Falk A. Toward Standardised iPSC Testing: Insights from a Multi-Year International Quality Assessment Round. Stem Cell Reports 21, 102857; 2026.
- hPSCreg. (n.d.). Cell registration. European Human Pluripotent Stem Cell Registry. <https://hpscereg.eu/about/registration>
- International Council for Harmonisation. (1997). Q5D: Derivation and characterisation of cell substrates used for production of biotechnological/biological products. <https://www.ich.org/page/quality-guidelines>
- International Council for Harmonisation. (1999). Q6B: Specifications: Test procedures and acceptance criteria for biotechnological/biological products. <https://www.ich.org/page/quality-guidelines>
- International Council for Harmonisation. (2022). Q13: Continuous manufacturing of drug substances and drug products. <https://www.ich.org/page/quality-guidelines>
- International Council for Harmonisation. (2023a). Q5A(R2): Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin. <https://www.ich.org/page/quality-guidelines>
- International Council for Harmonisation. (2023a). Q5 E Comparability of Biotechnological/Biological Products. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-e-comparability-biotechnologicalbiological-products-step-5_en.pdf
- International Council for Harmonisation. (2023b). Q9(R1): Quality risk management. <https://www.ich.org/page/quality-guidelines>
- International Council for Harmonisation. (2025). Recommendations with regard to future ATMP related guidelines output from cell & gene therapy discussion group (CGTDG) (2023-2025) https://database.ich.org/sites/default/files/ICH_CGTDG_RecommendationPaper_2025_1201_MCEndorsed_2_025_1117.pdf

- International Organization for Standardization. (2022). ISO 24603:2022 biotechnology — Biobanking — Requirements for human and mouse pluripotent stem cells. <https://www.iso.org/standard/79046.html>
- International Organization for Standardization. (2024). Biotechnology—Data interoperability for stem cell data—Part 1: Framework (ISO Standard No. 8472-1:2024). International Organization for Standardization.
- International Stem Cell Banking Initiative. (2009). Consensus guidance for banking and supply of human embryonic stem cell lines for research purposes. Stem Cell Reviews and Reports. <https://pubmed.ncbi.nlm.nih.gov/20016957/>
- International Stem Cell Banking Initiative. (2010). Human embryonic stem cell lines and their use in international research. Stem Cell Reviews and Reports. <https://pmc.ncbi.nlm.nih.gov/articles/PMC2952289/>
- International Stem Cell Initiative; Oluseun Adewumi, Behrouz Aflatoonian, Lars Ahrlund-Richter, Michal Amit, Peter W Andrews, Gemma Beighton, Paul A Bello, Nissim Benvenisty, Lorraine S Berry, Simon Bevan, Barak Blum, Justin Brooking, Kevin G Chen, Andre B H Choo, Gary A Churchill, Marie Corbel, Ivan Damjanov, Jon S Draper, Petr Dvorak, Katarina Emanuelsson, Roland A Fleck, Angela Ford, Karin Gertow, Marina Gertsenstein, Paul J Gokhale, Rebecca S Hamilton, Ales Hampl, Lyn E Healy, Outi Hovatta, Johan Hyllner, Marta P Imreh, Joseph Itskovitz-Eldor, Jamie Jackson, Jacqueline L Johnson, Mark Jones, Kehkooi Kee, Benjamin L King, Barbara B Knowles, Majlinda Lako, Franck Lebrin, Barbara S Mallon, Daisy Manning, Yoav Mayshar, Ronald D G McKay, Anna E Michalska, Milla Mikkola, Masha Mileikovsky, Stephen L Minger, Harry D Moore, Christine L Mummery, Andras Nagy, Norio Nakatsuji, Carmel M O'Brien, Steve K W Oh, Cia Olsson, Timo Otonkoski, Kye-Yoon Park, Robert Passier, Hema Patel, Minal Patel, Roger Pedersen, Martin F Pera, Marian S Piekarczyk, Renee A Reijo Pera, Benjamin E Reubinoff, Allan J Robins, Janet Rossant, Peter Rugg-Gunn, Thomas C Schulz, Henrik Semb, Eric S Sherrer, Henrike Siemen, Glyn N Stacey, Miodrag Stojkovic, Hirofumi Suemori, Jin Szatkiewicz, Tikva Turetsky, Timo Tuuri, Steineke van den Brink, Kristina Vintersten, Sanna Vuoristo, Dorien Ward, Thomas A Weaver, Lesley A Young, Weidong Zhang (2007) Characterization of human embryonic stem cell lines by the International Stem Cell Initiative, Nat Biotechnol. 2007 Jul;25(7):803-16. doi: 10.1038/nbt1318. PMID: 17572666
- International Stem Cell Initiative; Katherine Amps, Peter W Andrews, George Anyfantis, Lyle Armstrong, Stuart Avery, Hossein Baharvand, Julie Baker, Duncan Baker, Maria B Munoz, Stephen Beil, Nissim Benvenisty, Dalit Ben-Yosef, Juan-Carlos Biancotti, Alexis Bosman, Romulo Martin Brena, Daniel Brison, Gunilla Caisander, María V Camarasa, Jieming Chen, Eric Chiao, Young Min Choi, Andre B H Choo, Daniel Collins, Alan Colman, Jeremy M Crook, George Q Daley, Anne Dalton, Paul A De Sousa, Chris Denning, Janet Downie, Petr Dvorak, Karen D Montgomery, Anis Feki, Angela Ford, Victoria Fox, Ana M Fraga, Tzvia Frumkin, Lin Ge, Paul J Gokhale, Tamar Golan-Lev, Hamid Gourabi, Michal Gropp, Guangxiu Lu, Ales Hampl, Katie Harron, Lyn Healy, Wishva Herath, Frida Holm, Outi Hovatta, Johan Hyllner, Maneesha S Inamdar, Astrid Kresentia Irwanto, Tetsuya Ishii, Marisa Jaconi, Ying Jin, Susan Kimber, Sergey Kiselev, Barbara B Knowles, Oded Kopper, Valeri Kukhareenko, Anver Kuliev, Maria A Lagarkova, Peter W Laird, Majlinda Lako, Andrew L Laslett, Neta Lavon, Dong Ryul Lee, Jeoung Eun Lee, Chunliang Li, Linda S Lim, Tenneille E Ludwig, Yu Ma, Edna Maltby, Ileana Mateizel, Yoav Mayshar, Maria Mileikovsky, Stephen L Minger, Takamichi Miyazaki, Shin Yong Moon, Harry Moore, Christine Mummery, Andras Nagy, Norio Nakatsuji, Kavita Narwani, Steve K W Oh, Sun Kyung Oh, Cia Olson, Timo Otonkoski, Fei Pan, In-Hyun Park, Steve Pells, Martin F Pera, Lygia V Pereira, Ouyang Qi, Grace Selva Raj, Benjamin Reubinoff, Alan Robins, Paul Robson, Janet Rossant, Ghasem H Salekdeh, Thomas C Schulz, Karen Sermon, Jameelah Sheik Mohamed, Hui Shen, Eric Sherrer, Kuldip Sidhu, Shirani Sivarajah, Heli Skottman, Claudia Spits, Glyn N Stacey, Raimund Strehl, Nick Strelchenko, Hirofumi Suemori, Bowen Sun, Riitta Suuronen, Kazutoshi Takahashi, Timo Tuuri, Parvathy Venu, Yuri Verlinsky, Dorien Ward-van Oostwaard, Daniel J Weisenberger, Yue Wu, Shinya Yamanaka, Lorraine Young, Qi Zhou (2011) Screening ethnically diverse human embryonic stem cells identifies a chromosome 20 minimal amplicon conferring growth advantage Nat Biotechnol. 29(12):1132-44. doi: 10.1038/nbt.2051. PMID: 22119741 PMCID: PMC3454460
- International Society for Stem Cell Research. (2021). Guidelines for stem cell research and clinical translation. Stem Cell Reports, 16(6), 1398–1408. <https://pubmed.ncbi.nlm.nih.gov/34048692/> [Note: this citation refers to a summary article. The full 2021 ISSCR Guidelines document is available at: <https://www.isscr.org/guidelines>]

- International Society for Stem Cell Research. (2023). Standards for human stem cell use in research. <https://www.isscr.org/basic-research-standards>
- Japan. (2014). Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act). Ministry of Health, Labour and Welfare. <https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/>
- Kellathur SN, Garbe JHO, Beattie SG, O'Kane M, Litsiou A, Ho K, Adam S, Muralidharan S, Hussain M. An analysis of advanced therapy medicinal products regulatory landscape in ICH member countries: opportunities and challenges. *Cell & Gene Therapy Insights*. 2026;12(1):117–134. doi:10.18609/cgti.2026.016.
- Kim J-H, Kawase E, Bharti K, Karnieli O, Arakawa Y, Stacey G (2022) Perspectives on the cost of goods for hPSC banks for manufacture of cell therapies. *NPJ Regen Med*. 2022 Sep 29;7(1):54. doi: 10.1038/s41536-022-00242-7. PMID: 36175440 PMCID: PMC9522845
- Kim J-H, Kurtz A, Barbaric I, Inamdar MS, Pera MF, Benvenisty N, Shakiba N, Isasi R, Hanatani T, Stacey G (2026) Perspectives from the 2025 ISCB/ISCI joint workshop on genetic stability, clonal monitoring, ethical data governance, and global inclusion in stem cell banking. *Stem Cell Res Therapy*. 17(1):2. doi: 10.1186/s13287-025-04797-2. PMID: 41484925 PMCID: PMC12764013
- Kim, YJ., Kang, B., Kweon, S. et al. Longitudinal analysis of genetic and epigenetic changes in human pluripotent stem cells in the landscape of culture-induced abnormality. *Exp Mol Med* 56, 2409–2422 (2024). <https://doi.org/10.1038/s12276-024-01334-8>
- Kobold S, Buttjer N, Stacey GN, Mueller SC, Kurts A, Mah N. (2023). History and current status of clinical studies using human pluripotent stems. Vol. 18 j 1–7 j July 11, 2023 <https://doi.org/10.1016/j.stemcr.2023.03.005>
- Korea Ministry of Government Legislation. (2024). Act on the Safety of and Support for Advanced Regenerative Medicine and Advanced Biological Products. https://elaw.klri.re.kr/eng_mobile/viewer.do?hseq=68827&type=part&key=37
- Lee S, Ji Young Huh, David M. Turner, Soohyeon Lee, James Robinson, Jeremy E. Stein, Sung Han Shim, Chang Pyo Hong, Myung Seo Kang, Masato Nakagawa, Shin Kaneko, Mahito Nakanishi, Mahendra S. Rao, Andreas Kurtz, Glyn N. Stacey, Steven G.E. Marsh, Marc L. Turner, Jihwan Song, (2018) Repurposing the Cord Blood Bank for Haplobanking of HLA-Homozygous iPSCs and Their Usefulness to Multiple Populations, *Stem Cells*, 2018;36:1552-1566. <https://doi.org/10.1002/stem.2865>
- Liang G, Zhang Y. Genetic and epigenetic variations in iPSCs: potential causes and implications for application. *Cell Stem Cell*. 2013 Aug 1;13(2):149-59. doi: 10.1016/j.stem.2013.07.001. PMID: 23910082; PMCID: PMC3760008.
- Mah N, Seltmann S, Aran B, Steeg R, Dewender J, Bultjer N, Veiga A, Stacey G, Kurtz A, Access to stem cell data and registration of pluripotent cell lines: the Human Pluripotent Stem Cell Registry (hPSCreg), *Stem Cell Research* (2020), doi: <https://doi.org/10.1016/j.scr.2020.101887>
- Ministry of Health, Labour and Welfare (Japan). (2024). Basic policy on evaluation of efficacy following conditional and time-limited approval of regenerative medical products [Policy document, in Japanese]. Tokyo: MHLW. [No English-language URL available; Japanese-language document available at: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryuu/iyakuhin/saisei_iryuu/index.html]
- NMPA. (2025). Announcement on optimising the review and approval process for clinical trials of innovative drugs ([2025] No. 86). National Medical Products Administration (China). <https://english.nmpa.gov.cn/>
- O'Shea O, Chapman C, Klair H, Abranches E, Vessillier S, De Jesus Saraiva L, Rigsby P, Price J, et al. (2019) Collaborative study to assess the suitability of the candidate WHO International Reference Reagent for MSC identity (for flow cytometry) for advanced therapies. WHO/BS/2019.2376. Geneva: World Health Organization;
- O'Shea O, Steeg R, Chapman C, MacKintosh P, Stacey GN (2020) Development and Implementation of Large-scale Quality Control for the European Bank for Induced Pluripotent Stem Cells. *Stem Cell Research*. *Stem Cell Research* 45:101773. DOI: 10.1016/j.scr.2020.101773

- Pamies D, Leist M, Coecke S, Bowe G, Allen DG, Gstraunthaler G, Bal-Price A, Pistollato F, de Vries RBM, Hogberg HT, Hartung T, Stacey GN (2022). Guidance document on Good Cell and Tissue Culture Practice 2.0 (GCCP 2.0). ALTEX. 2022;39:30-70. doi: 10.14573/altex.2111011. PMID: 34882777.
- Pharmaceuticals and Medical Devices Agency. (n.d.). Regenerative medical products. <https://www.pmda.go.jp/english/review-services/reviews/0003.html>
- Pharmaceuticals and Medical Devices Agency. (2016, June 26). Technical guidance for quality, nonclinical safety studies and clinical studies for the products derived from processed human or animal cells. <https://www.pmda.go.jp/files/000273883.pdf>
- Ricupero CL, Swerdel MR, Hart RP. Epigenome analysis of pluripotent stem cells. *Methods Mol Biol.* 2013;997:203-16. doi: 10.1007/978-1-62703-348-0_16. PMID: 23546758; PMCID: PMC4431589.
- Simon, C.G., Bozenhardt, E.H., Celluzi, C., Dobnik, D., Grant, M.L., Lakshmipathy, U., Nebel, T., Peltier, L., Ratcliffe, A., Sherley, J.L., Stacey, G.N., Taghizadeh, R.R., Tan E.H.P., Vessilier S. (2024) Mechanism of action, potency and efficacy: considerations for cell therapies. *J Transl Med* 22, 416 DOI: 10.1186/s12967-024-05179-7
- Simon, C.G., Bozenhardt, E.H., Celluzzi, C.M. David Dobnik, Melanie L. Grant, Uma Lakshmipathy, Thiana Nebel, Linda Peltier, Anthony Ratcliffe, James L. Sherley, Glyn N. Stacey, Rouzbeh R. Taghizadeh, Eddie H. P. Tan, Sandrine Vessillier (2025). Analysis of the measurements used as potency tests for the 31 US FDA-approved cell therapy products. *J Transl Med* 23, 259. <https://doi.org/10.1186/s12967-025-06253-4>
- Sullivan S, Stacey GN, Akazawa C, Aoyama N, Baptista R, Bedford P, Bennaceur Griscelli A, Chandra A, Elwood N, Girard M, Kawamata S, Hanatani T, Latsis T, Lin S, Ludwig TE, Malygina T, Mack A, Mountford JC, Noggle S, Pereira LV, Price J, Sheldon M, Srivastava A, Stachelscheid H, Velayudhan SR, Ward NJ, Turner ML, Barry J, Song J. (2018) Quality control guidelines for clinical-grade human induced pluripotent stem cell lines. *Regen Med.* 2018 Oct;13(7):859-866. doi: 10.2217/rme-2018-0095. Epub 2018 Sep 12.
- Warre Cornish, K, Perfect L, Lindsay Hill L, Bako L, Mattioli E, Wise, C. Carpenter L., Burns C. (2024) Developing reference reagents to assure the quality of mesenchymal stromal cell therapies, *Cytotherapy*, 26, Supplement, 2024, Pages S70-S71, <https://doi.org/10.1016/j.jcyt.2024.03.126>.
- Wilson KD, Venkatasubrahmanyam S, Jia F, Sun N, Butte AJ, Wu JC. MicroRNA profiling of human-induced pluripotent stem cells. *Stem Cells Dev.* 2009 Jun;18(5):749-58. doi: 10.1089/scd.2008.0247. PMID: 19284351; PMCID: PMC3135181.
- World Health Organization. (2013). Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks, (WHO Technical Report Series No. 978, Annex 3) <https://www.who.int/publications/m/item/animal-cell-culture-trs-no-978-annex3>
- World Health Organization. (2023a). Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products (WHO Technical Report Series No. 1048, Annex 3). <https://cdn.who.int/media/docs/default-source/biologicals/annex-3---hcts-atmps-regulatory-considerations---clean-for-posting---13-dec-2023.pdf>
- World Health Organization. (2023b). Cell, tissue and gene therapy products. <https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards/cell--tissue-and-gene-therapy-products>