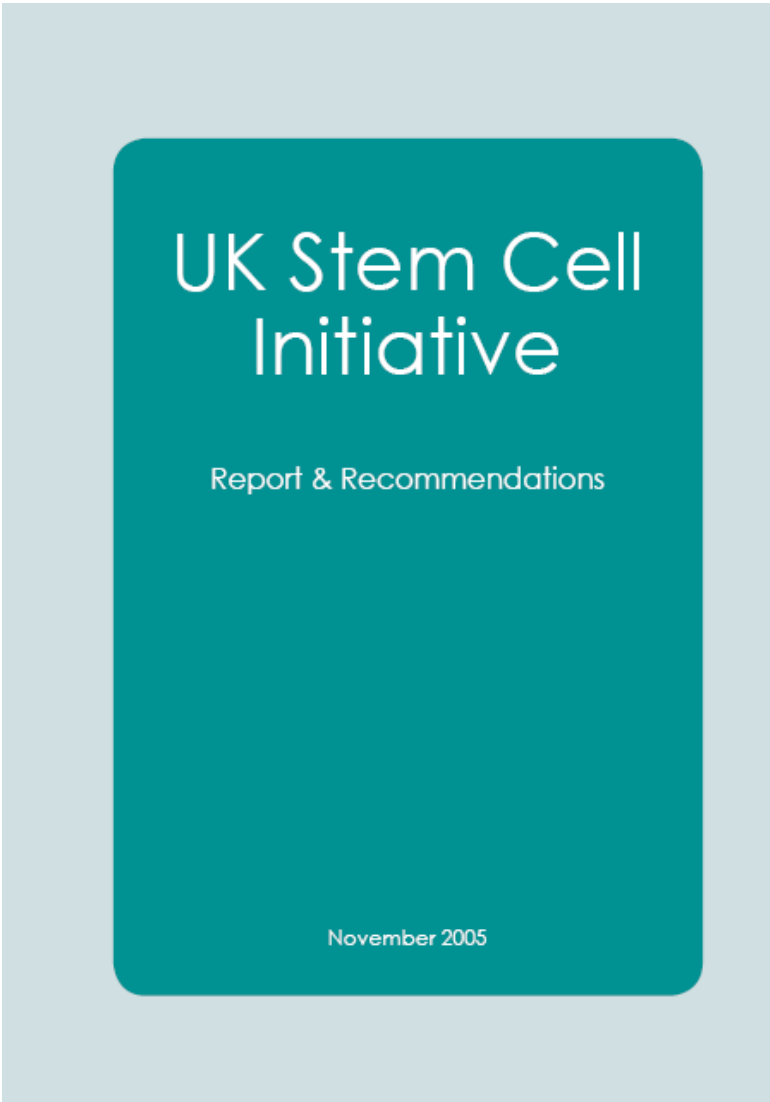
The UK Stem Cell Initiative
('The Pattison Report')

John Connolly PhD
Cell & Gene Therapies Team
Health, Science & Bioethics Division

DH Department of Health

UKSCI: The Pattison Report



UK Stem Cell Initiative (UKSCI) was established by the then Chancellor, Rt. Hon. Gordon Brown, in his March 2005 Budget. UKSCI was charged with developing a ten-year vision and costed strategy for UK stem cell research, for implementation between 2006-2015

Chairman:
Sir John Pattison DM FRCPath FMedSci

Panel Members:
Professor Colin Blakemore, Chief Executive, Medical Research Council (Alternate: Dr Diana Dunstan);
Professor Julia Goodfellow, Chief Executive, Biotechnology & Biological Sciences Research Council;
Professor Sally Davies, Director of R&D, Department of Health;
Dr Mark Walport, Director, The Wellcome Trust;
Dr Fiona Watt, The Academy of Medical Sciences;
Ms Diana Garnham, Chief Executive, Association of Medical Research Charities;
Dr Peter Mountford, Chief Executive, Stem Cell Sciences Ltd.;
Dr Peter Arnold, Director of Technology, Smith and Nephew (UK);
Dr David McCauley, Chief Executive, UK Stem Cell Foundation;
Sir Christopher Evans, Trustee, UK Stem Cell Foundation;
Lord May of Oxford, Trustee, UK Stem Cell Foundation.

Secretariat:
Dr John Connolly, Department of Health

Key Drivers in 2005

- UK Stem Cell Foundation emerges
- Proposition 71 establishes CIRM
- S. Korea marches ahead at cloning
- NHS R&D Investment Concerns
- Reluctance of Big Pharma
- HFE Act to be reviewed

Box 9
SWOT analysis of UK Stem Cell Research

Strengths

- Supportive and consistent Government position
- Enabling regulation for embryonic stem cell research
- Favourable ethical environment & public support
- World-class academic researchers in developmental and reproductive biology
- Strong climate of innovation in UK
- UK Stem Cell Bank
- National Blood Service
- Estimated £30M per annum investment in UK stem cell research from public and charity sector funding bodies
- Strong bio-processing initiative
- Strong clinical trials base and UKCRC

Weaknesses

- Gaps in UK funding for translational research
- Unknown business model & return on investment
- Lack of involvement by big pharmaceutical companies
- Lack of venture capital investment
- Lack of regulatory clarity for clinical use of stem cell therapies
- Lack of central co-ordinated strategy leading to "cottage industry" approach
- Smaller science base than US
- History of innovations being lost to the US for commercialisation phase
- Lack of clarity on Intellectual Property and Licensing Issues

Opportunities

- World leadership in embryonic stem cell therapies
- Enhanced drug development & cancer research
- Use NHS to drive clinical translation
- Redirect UK researchers from developmental biology to stem cell research
- Public investment matched by private funding
- Attract foreign skills as international hub
- Drive international agenda
- Attract international inward investment
- Develop international alliances

Threats

- Lack of infrastructure impedes clinical translation
- 'Brain-drain' to US & Far East
- Intellectual Property captured in US & Far East
- UK biotechnology sector weakens
- EU moves to limit stem cell research
- Clinical trial adverse events unravels public support
- NHS has to import expensive stem cell treatments for care of aging population

Broad UKSCI themes

UKSCI has identified five major themes for development, to maintain and increase the momentum of UK stem cell research over the next decade:

- **A Public-Private Consortium in the UK for the Advancement of Stem Cell Technology:** The establishment of consortium of pharmaceutical, healthcare and biotechnology companies with the UK Government to develop stem cells as a resource for discovery in medicine.

- **Extension of the Capacity of UK Stem Cell Research**: Fortification of infrastructure needed to develop stem cell therapy via support for Centres of Excellence, the UK Stem Cell Bank and Cell Therapy Production Units.

- **Consolidation of Research Funding for UK Stem Cell Research**: The development of the UK as a centre for translational and clinical stem cell research, with the help of a public-private partnership between the Government and the *UK Stem Cell Foundation*, along with continuing strategic investment in basic stem cell research via the Research Councils and private funding bodies.

- **Judicious Regulatory Measures to Enable UK Stem Cell Research**: The favourable regulatory climate in the UK for stem cell research should be extended to include clinical applications.

- **Enhanced Coordination & Communication of UK Stem Cell Research**: More coordinated activities between Government bodies, research councils and stem cell researchers and increased dialogue with the public over the next decade on stem cell research.

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SC4SM

Stem Cells for Safer Medicines

Founding Consortium Members

Private sector

- AstraZeneca
- GlaxoSmithKline
- Hoffman La Roche

More in discussion to join

- Target of 5-6 members

Government

- BBSRC
- Dept of Health
- DIUS
- MRC
- Scottish Government
- Coordinated via TSB

Attrition of compounds during clinical development – main reasons for failure

- Review of reasons for late stage attrition was carried out by the ABPI's Safety Biomarker Working Group
- In total 240 drugs were analysed
- The summary does not classify the therapeutic area, solely the organ and pathology of the adverse drug reaction is expressed

ORGAN	No.
Cardiovascular	64
Liver	42
Musculoskeletal	15
Immune system	13
Kidney	12
CNS	10
Testes	10
Gastro-intestinal	8
Eye	7
Genetic toxicology	7
Reproductive toxicity	7

Data from ABPI's Biomarker Working Group, 2007

SC4SM
Stem Cells for Safer Medicines

Stem Cells for Safer Medicines

Is a public-private collaboration whose objective is:

To enable the creation a bank of stem cells, open protocols and standardised systems in stem cell technology that will enable consistent differentiation of stem cells into stable homogenous populations of particular cell types, with physiologically relevant phenotypes suitable for toxicology testing in high throughput platforms.

SC4SM
Stem Cells for Safer Medicines

Stem Cells for Safer Medicines

Target:

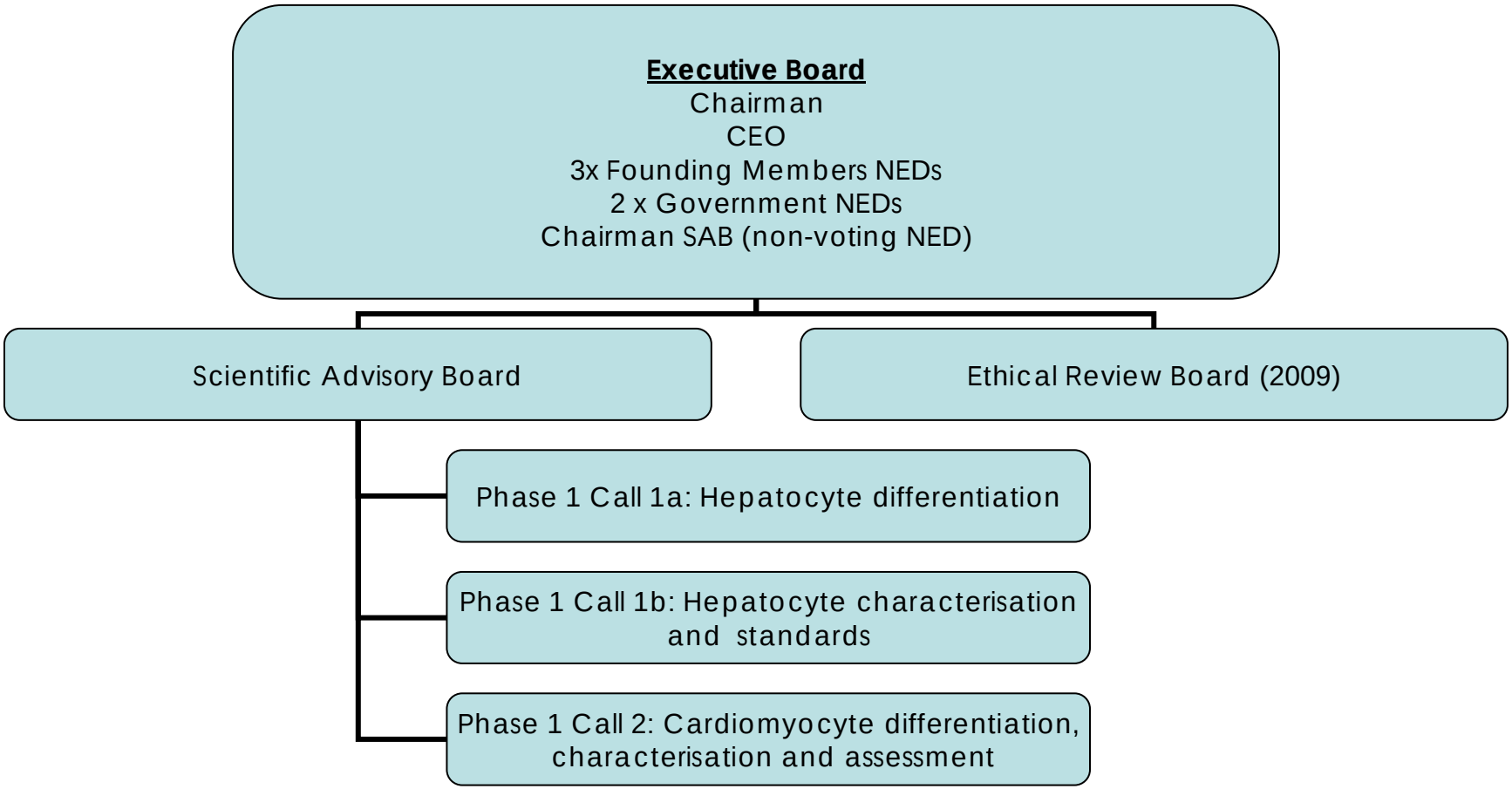
To develop 2 or more medium to high throughput screens for early predictive toxicology to reduce risk in clinical development and to make substantive progress in developing long-term chronic screens utilising complex systems

- –focused on hepato- and cardio-toxicity
- –range of cell lines with key genotypes
- – standardised compounds for positive and negative controls
- –integrating number of platform technologies

SC4SM

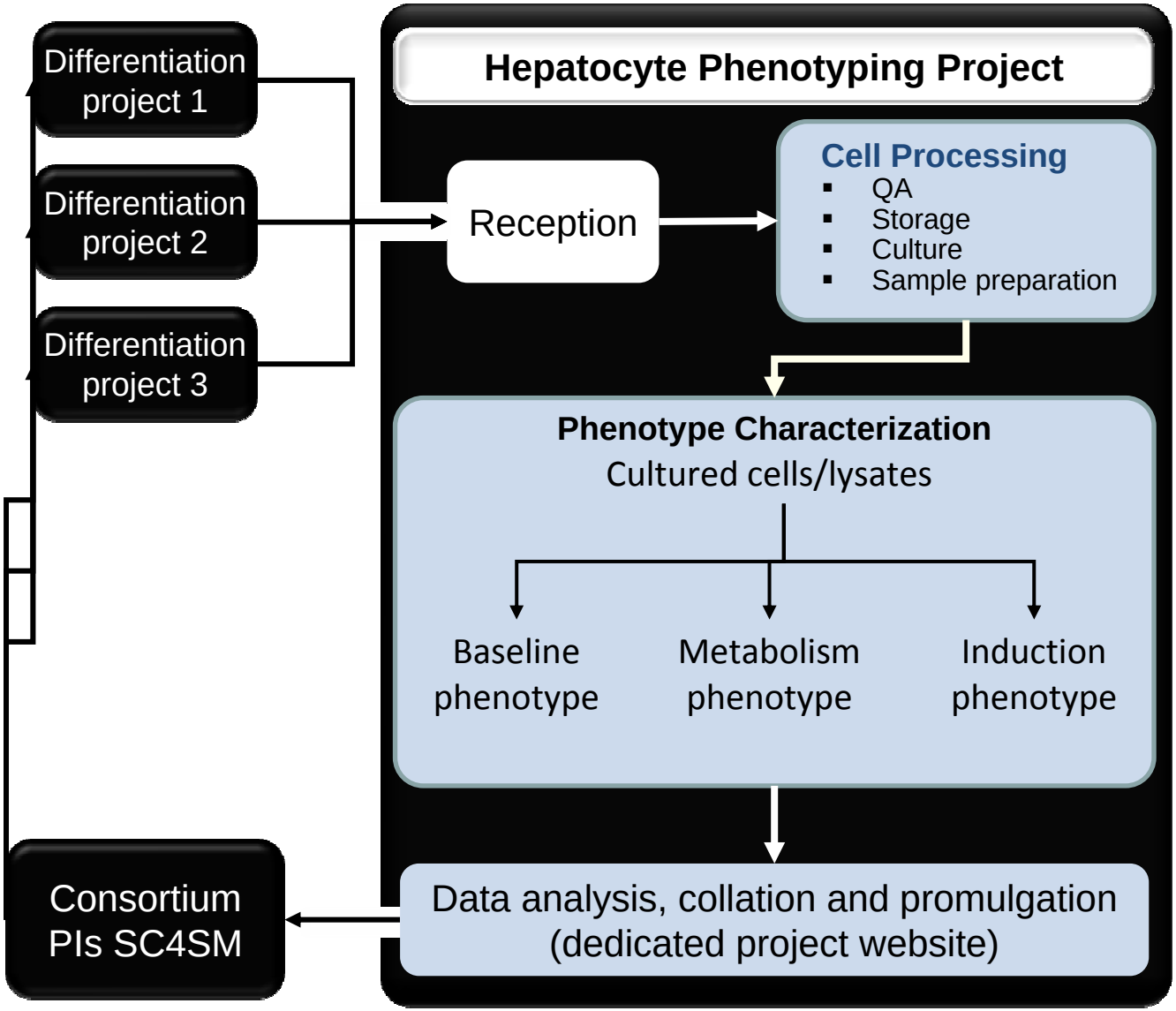
Stem Cells for Safer Medicines

SC4SM Structure



SC4SM
Stem Cells for Safer Medicines

Overview of Cell Phenotyping Project



SOURCE: Chris Goldring, University of Liverpool

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UK Stem Cell Bank

- MRC & BBSRC have agreed proposals for phase 2 development
- Consolidate the Bank's operations in new permanent facilities
- Provide GMP facilities for the derivation of clinical grade stem cell lines
- Plans are currently being implemented with building in progress
- Five year operational funding has been awarded, amounting to a total funding commitment of £9.2m (MRC £8.2m, BBSRC £1m)

UK StemCellBank

UK Stem Cell Bank

- 64 human ES cell (hESC) lines have been or are in the process of being deposited in the Bank to date, both from UK and overseas groups

- 15 quality-controlled hESC lines currently available to community

- 18 due for release soon

- Efforts are also ongoing to increase the Bank's profile internationally, and have been committed to website development and the development of international links and harmonisation of standards.

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Centres of Excellence

- MRC has significant intramural investments in stem cells its institutes in Oxford and London (NIMR and CSC Hammersmith)
- MRC Centre Development Grants have been awarded to Edinburgh. Scottish Executive announced a £59 million investment in a Scottish Centre for Regenerative Medicine (SCRM) at Edinburgh University. This will bring basic scientific research, clinical development and commercial application together in one building and provide state-of-the-art research facilities, manufacturing capacity and commercialisation facilities.
- MRC Centre Development Grants have also been awarded to Cambridge. Cambridge investment is part of a broader activity to support the Institute of Stem Cell Medicine at Cambridge, in conjunction with the Wellcome Trust, and towards which MRC has provided capital investment for the construction of GMP facilities.
- ESRC funds 3 Centres through its genomics network which address stem cell issues (in Cardiff, Edinburgh and Exeter).
- BBSRC also supports a number of interdisciplinary programmes of activity through research grants.
- The RCs will continue to proactively monitor this, with the expectation that further core support will be provided for these and emerging Centres in future years.

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Cell Therapy Production Facilities

- GMP facilities for the generation of clinical grade embryonic stem cell lines have been funded by MRC and DH at six centres around the UK
- In Cambridge, MRC has provided capital investment for the construction of GMP facilities
- GMP facilities under construction in Edinburgh
- GMP facilities also under construction at the UK Stem Cell Bank with facilities for 'hotel' function

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Government Spend On Stem Cell Research

Organisation	03/04	04/05	05/06	06/07	07/08
DIUS (DTI)	0	1,857,866	1,857,866	1,696,113	1,325,899
Research Councils	11,368,269	15,378,451	12,646,173	26,600,000	24,300,000
CSO Scotland	76,147	127,180	n.a.	n.a.	n.a.
Scottish Enterprise	0	338,953	316,000	1,675,000	1,200,000
R&D Office of N. Ireland	280,992	255,584	241,547	91,825	34,827
Wales Office of R&D (WORD)	448,114	1,250,658	1,683,657	2,804,528	2,341,267
DH National Research Registry data	0	6,500,000	7,000,000	7,500,000	8,000,000
RDAs	750,000	2,050,000	4,165,000	8,375,000	5,200,000
Total	**12,923,522**	**27,758,692**	**27,910,243**	**48,742,466**	**42,401,993**

The RDA figure includes LDA's £5million for the Foundation and the Scottish Enterprise contribution. The figure is an overall figure for research and does not include: Stem cell bank figures; Rec 1 Public Private Partnership – Stem Cells for Safer Medicines (£700K in 2006-07) and £1.3 million in DIUS (DTI) figures for meterological issues, and regenerative medicine technologies; Rec 8 – any costs associated with regulation/ethical oversight; Rec 9, 10 and 11 – some of the cost of communication/ collaboration/ networking may come from Research Council's basic research spend. The DH figure for 2004-05 is a rough estimate for R&D in the NHS and the NHSBT based on data from the National Research Register. Figures for subsequent years are projected on the basis of that estimate.

Translational Funding

- The Translational Stem Cell Research Committee (TSCRC) has been established as the main vehicle for providing MRC support for high quality research aiming to apply stem cell technology to improve human health.
- The MRC delivery plan has the stated goal of funding translational stem cell research to a level of £10 million per annum by 2010/11.
- The TSCRC will build upon MRC's previous experience of working jointly with the UK Stem Cell Foundation (UKSCF) who remain engaged with this funding stream and will seek to identify co-funding opportunities where possible.
- The UKSCF is supporting a clinical trial study assessing the use of adult stem cells in patients suffering from a myocardial infarction.
- The DH R&D budget for the NHS for 2008-09 was £792 million - 3.5% higher in real terms than in 2007-08. This pattern of increases in government funding for health research will continue across the 2007 CSR period.

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Human Fertilisation and Embryology Act 2008

- Amends the 1990 Act
- Maintains the key principles of ‘necessary or desirable’ & 14 day limit
- Specifies that human admixed embryos can be created
- Specifics that the genetic structure of embryos can be altered
- Reinforces the principle of consent (subject to some exceptional circumstances)

Ethical Oversight of Stem Cell Clinical Research

The Gene Therapy Advisory Committee (GTAC) oversees the ethical conduct of stem cell and gene therapy clinical trials in the UK. Since 1st May 2008:

GTAC's Terms of Reference are

- To consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks.
- To consider and advise on the acceptability of proposals for research on human subjects using cells derived from stem cell lines, based on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks.
- To provide ethical advice on the use of unlicensed gene therapy and stem cell line derived therapies in humans.
- To work with other agencies which have responsibilities in this field, including research ethics committees, and agencies with statutory responsibilities - the Medicines and Healthcare products Regulatory Agency, the Human Tissue Authority, the Health and Safety Executive and the Department for Environment Food and Rural Affairs.
- To provide advice to United Kingdom Health Ministers on the above matters.

GTAC

Gene Therapy Advisory Committee

Points-to-consider for GTAC proposals

1. Preclinical studies:
   - Efficacy, safety, MOA
   - Tumourogenicity

2. Characterisation of cells:
   - Reliability in vitro and in vivo
   - Heterogeneity, differentiation, purity

3. Immunology:
   - Immunosuppression, tissue-matching, tolerance
   - Patient group co-morbidities

4. Genetic Stability:
   - Level of analysis, restriction of passage number?
   - Biological consequences?

5. Xenogenic issues:
   - Mouse Feeders

6. Use of Suicide & Marker Genes

7. Choice of Patient Population
   - Risk to benefit, number of years remaining, morbidity and mortality outlook

8. 'Expected Harm'= Probability X Magnitude
   - How can patients be informed about unknown or unquantifiable risks?

The Interim UK Regulatory Route Map for Stem Cell Research & Manufacture

Developed by:

- Department of Health
- Gene Therapy Advisory Committee,
- Health & Safety Executive,
- Home Office,
- Human Fertilisation & Embryology Authority,
- Human Tissue Authority,
- Medicines & Healthcare products Regulatory Agency,
- Medical Research Council,
- NHS Blood & Transplant Authority,
- Scottish National Blood Transfusion Service,
- SaBTO (Advisory Committee on the Safety of Blood, Tissues & Organs), &
- UK Stem Cell Bank.

A more detailed, user-friendly, web-based version of the map - from the 'toolkits' stable - is currently being developed and will be available by the end of 2009. In the meantime, feedback on this map can be sent to: *gtac@dh.gsi.gov.uk*

About the Map

In general, it will not be possible to determine with any degree of certainty the exact regulatory route for a given application without first consulting directly with the appropriate regulatory bodies. To establish the most appropriate regulatory route for a given stem cell therapy, there are a number of key questions to consider first. These are:

Q1. Are the stem cells intended for Human Application?
Discuss with the HTA (enquiries@hta.gov.uk)

Q2. Will the stem cells be derived from Human Embryo?
Discuss with the HFEA (admin@hfea.gov.uk)

Q3. Will the cells be Genetically Modified?
Discuss with the HSE (Notificationofficer@hse.gsi.gov.uk)

Q4. Will the stem cells be manufactured into a Medicinal Product or Investigational Medicinal Product? *Discuss with the MHRA (info@mhra.gsi.gov.uk)*

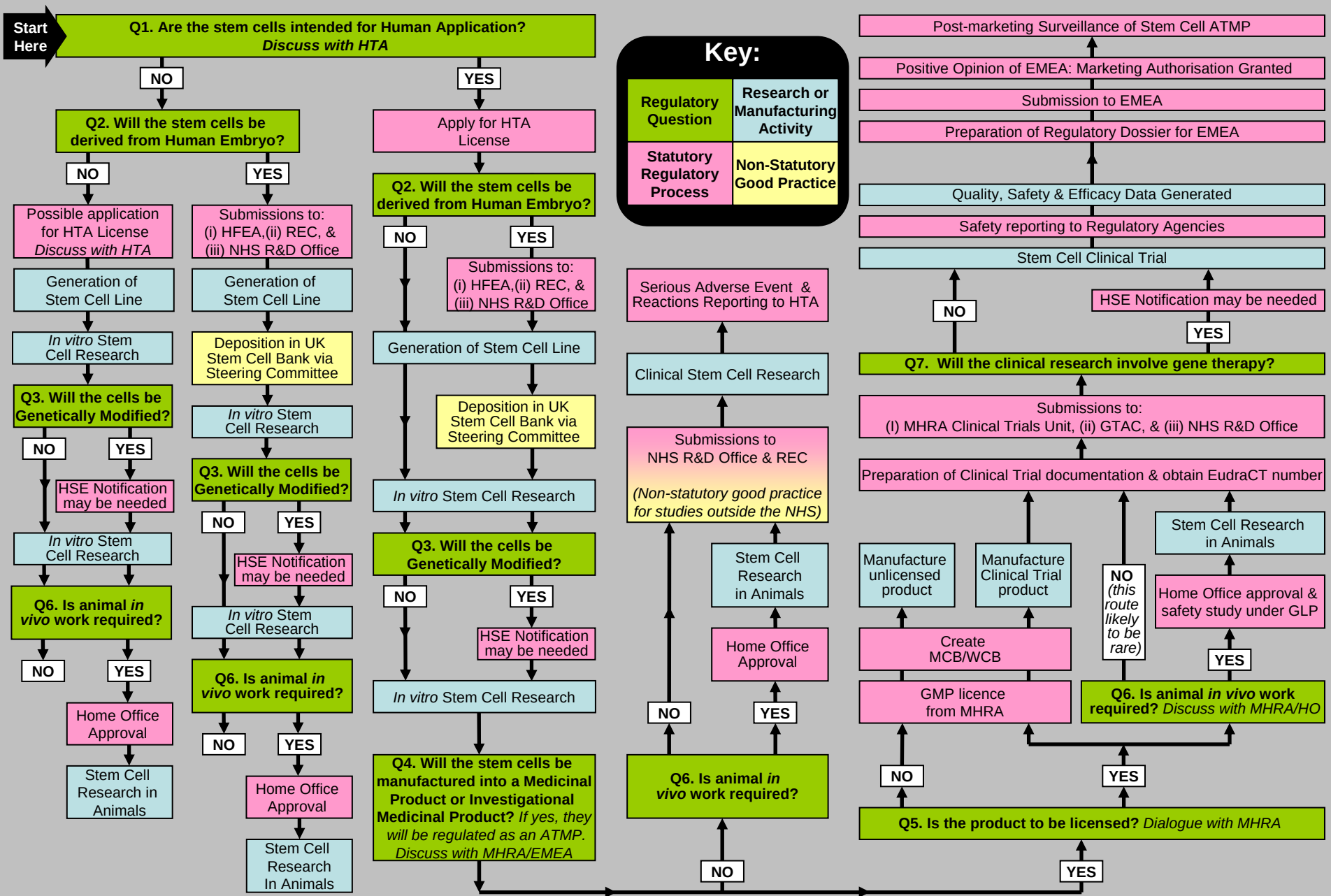
Q5. Is the Product to be Licensed?
Discuss with the MHRA (info@mhra.gsi.gov.uk)

Q6. Is Animal *in vivo* work required?
Discuss with the MHRA (info@mhra.gsi.gov.uk) & Home Office *(020 7035 4785)*

Q7. Will the clinical research involve Gene Therapy?
Discuss with GTAC (gtac@dh.gsi.gov.uk)

Interim UK Regulatory Route Map for Stem Cell Research & Manufacture

Version: 12.03.09



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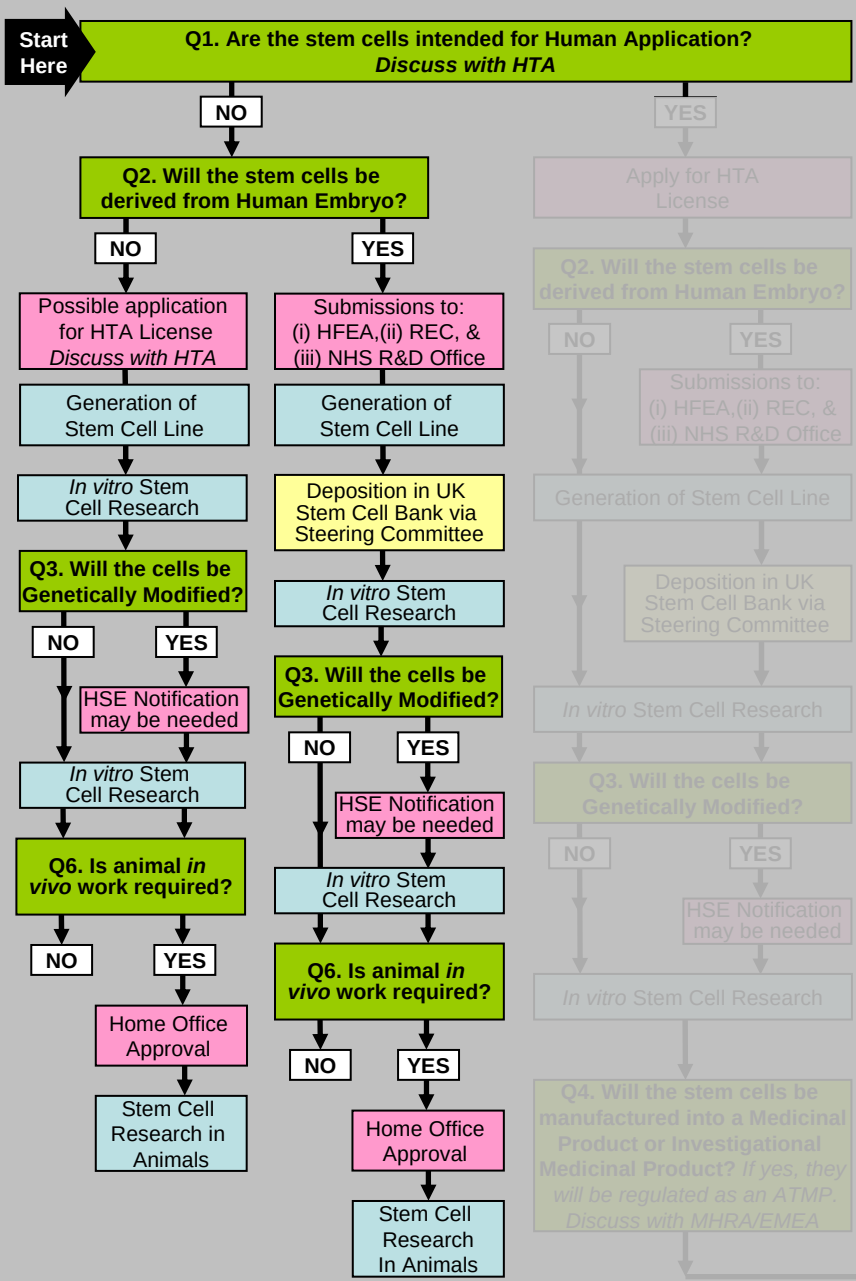

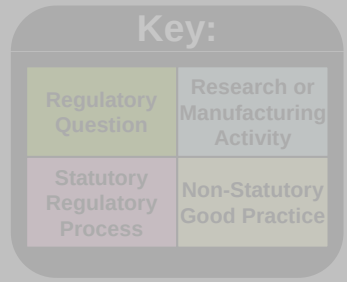

"The Basic Research Route"

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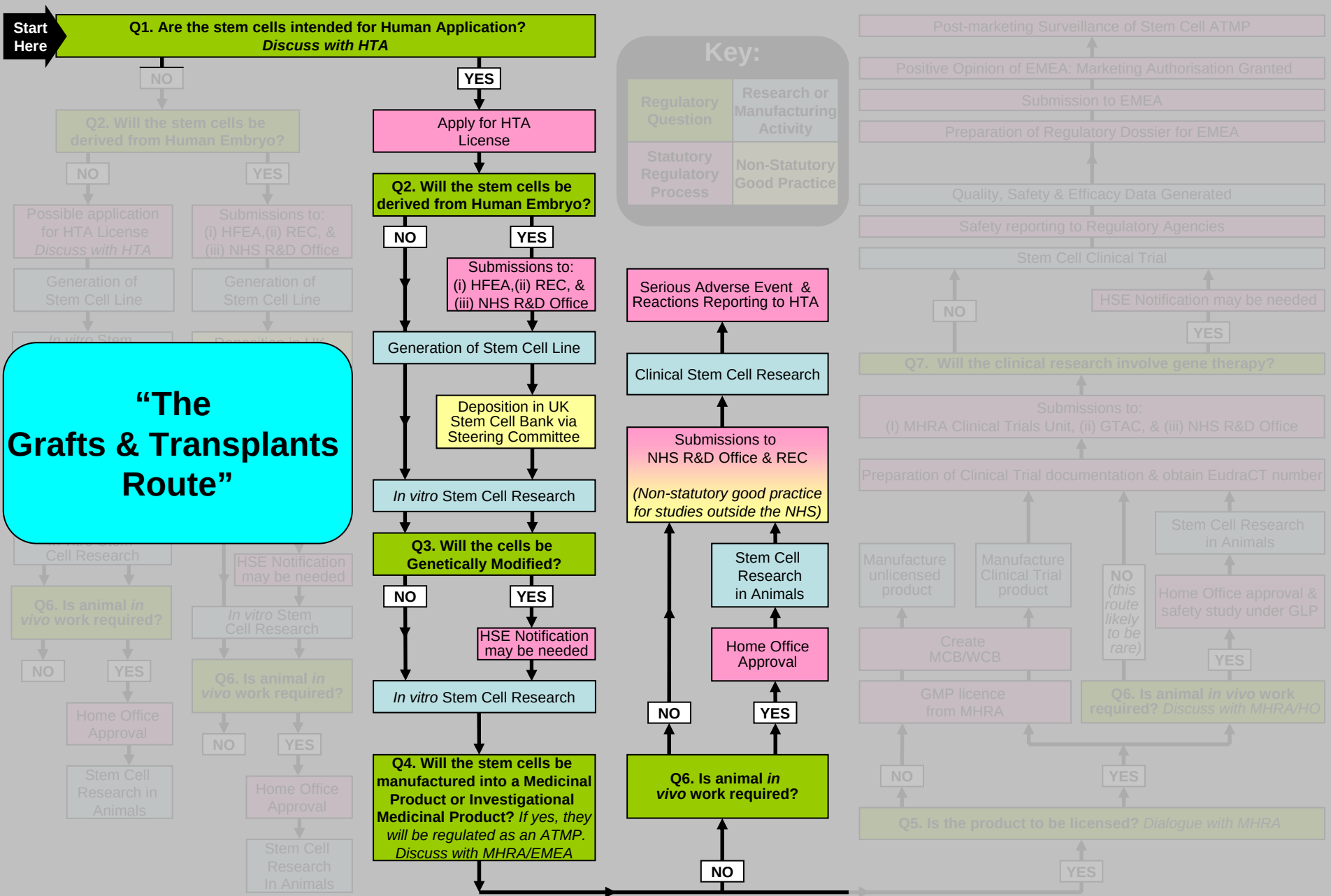

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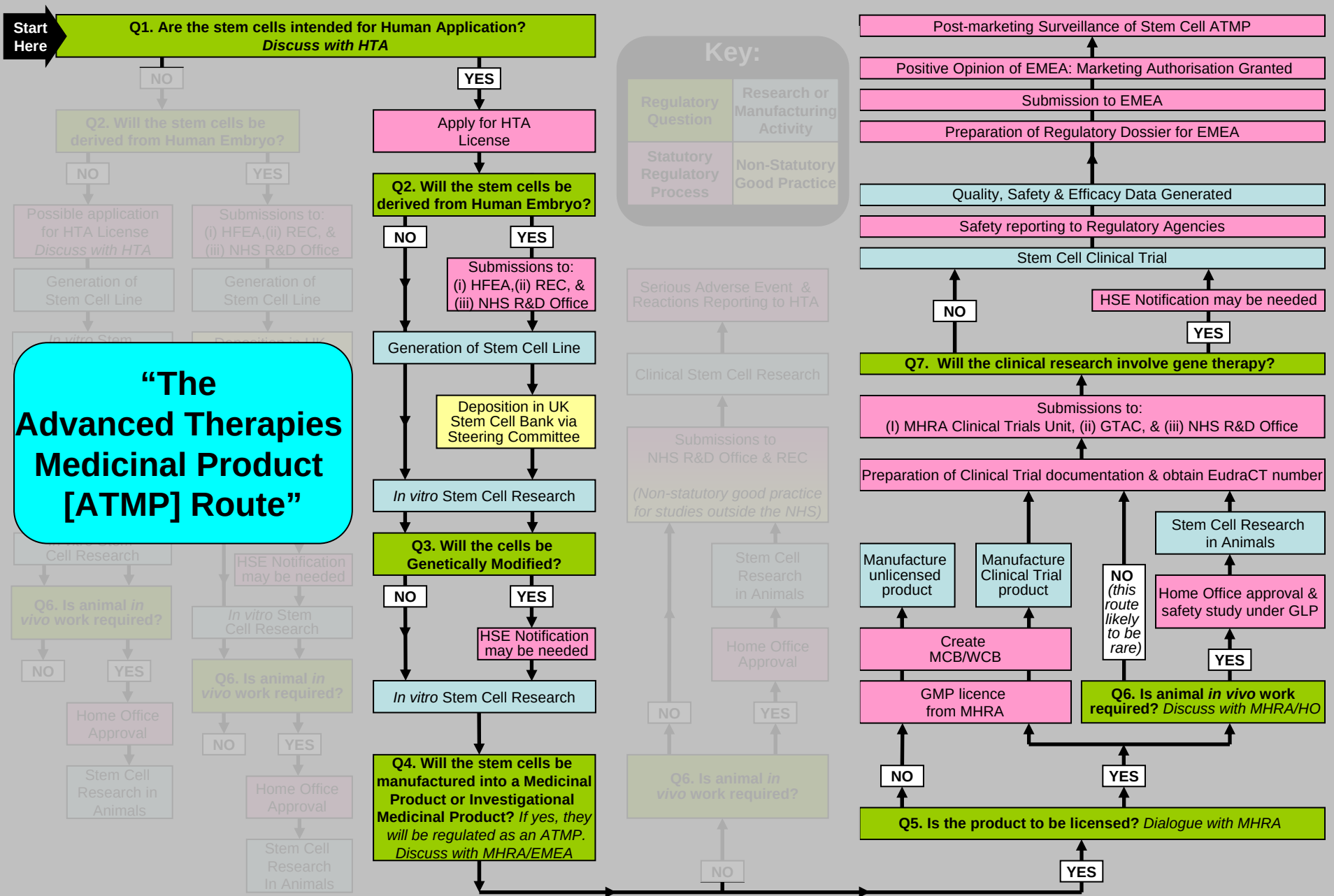

The 11 Recommendations of the UK Stem Cell Initiative

Recommendation 1: The UK Government should establish a public-private partnership to develop predictive toxicology tools for stem cell lines.

Recommendation 2: *The UK Stem Cell Bank* should be consolidated in new permanent facilities adjacent to its current site and its operational and development costs should be secured for the next decade**.**

Recommendation 3: The Research Councils should monitor the emergence of Centres of Excellence in stem cell research, designate them as such and strengthen them with core funding.

Recommendation 4: Research Councils and private sector funding bodies should support the development of stem cell therapy production units at UK Centres of Excellence in stem cell research.

Recommendation 5: The Government and Research Councils should strengthen the levels of funding for basic stem cell research over the next decade.

Recommendation 6: The Government should provide funding for clinical and translational stem cell research over the next decade at a level matching that raised by the UK Stem Cell Foundation (UKSCF), up to a maximum of £10M per annum, and administer it via a UKSCF/Medical Research Council collaboration.

Recommendation 7: The Department of Health must ensure that the promised increase in R&D resources is forthcoming and furthermore, that the full NHS costs of stem cell clinical research trials within the NHS are supported with extra funding from each Spending Review over the next decade to match the increase in research grants and activity.

Recommendation 8: The Government should continue to ensure that regulation of stem cell research is risk-based and proportionate and does not stifle the development of the full range of safe and effective new cell therapies for the benefit of patients. In particular, (i) the Department of Health should establish a specialised research ethics committee for stem cell clinical research; (ii) the Government should clarify the regulatory requirements for the use of animals and animal cells in human stem cell research; & (iii) for the *in* vitro use of embryonic stem cell lines, researchers should be registered with, and submit an annual research summary report to, the UK Stem Cell Bank.

Recommendation 9: The *UK Clinical Research Collaboration* should help to (i) coordinate organisations supporting stem cell research, including all of the relevant Research Councils and the UK Stem Cell Foundation and (ii) ensure that the *National Health Service* is optimally engaged in this area.

Recommendation 10: The Government should allocate additional funding to establish *The UK Stem Cell Cooperative*, to maximise the cross-fertilisation between those involved in the sub-disciplines of UK stem cell research.

Recommendation 11: The Research Councils, charitable funding bodies, and Government Departments should develop a sustained and coordinated programme of public dialogue on stem cell research over the next decade.

UK Stem Cell Funders Forum

- Under the aegis of the UKCRC, MRC has reconvened an expanded UK Stem Cell Funders Forum which is proactively co-ordinating all the key organisations supporting stem cell research in the UK.

- The Forum meets twice a year and in addition to UKCRC members includes senior representatives from ABPI, the Biosciences Association, RDAs and research charities.

- A key role for the Forum is to identify strengths and weaknesses in the UK stem cell research base and facilitate the targeting of future investment.

The 11 Recommendations of the UK Stem Cell Initiative

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UK National Stem Cell Network

- The UK NSCN successfully established has been in operation for approximately two years since 2006 after community meeting held in London.
- Network has hosted three national conferences in 2007, 2008 and 2009
- A major review of the activities of the Network was carried out at the end of 2008.
- The review involved a web-based questionnaire completed by those on the UK NSCN membership list and included follow-up discussions and interviews with selected representatives.
- **Recommendation 1:** UK NSCN should re-focus its objectives to prioritise its networking role.
- **Recommendation 2:** UK NSCN should appoint at least one more full time member of staff.
- **Recommendation 3**: UK NSCN should continue to be hosted by the Research Councils.
- **Recommendation 4:** Management Board to be established.
- **Recommendation 5:** Steering Committee modified to Advisory role.

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UK Stem Cell Communication Coalition

- UK Stem Cell Communication Coalition (SCCC) established.
- The coalition is made up of communication representatives from Research Councils (BBRSC, ESRC, EPSRC) major disease charities, Wellcome Trust, HFEA, HTA, Royal Society, Stem Cell Bank and DH.
- Chaired by MRC, which reports to the UK Stem Cell Funders Forum.
- The group's remit includes sharing information about each others' activities, keeping a watchful eye on issues in the media and trends in media coverage; and coordinating and initiating public dialogue activities. Recent and current activities of the Coalition's members have included:
- Public statements on stem cell tourism, Publication of a stem cell information pack, Stem cell exhibition and roadshow, Media Training Course, Public Dialogue in conjunction with Sciencewise

Landscape Changes Post Pattison

- The UK Stem Cell Foundation (UKSCF) impacts less than envisaged by Pattison
- The rise of induced Pluripotent Stem (iPS) cells
- The administration in the US has agreed to allow federal funding of embryonic stem cell research
- Increase in Stem Cell Tourism
- Increasing use and promise for cord blood stem cell applications
- DH's 'Best Research for Best Health' and ring-fenced investment in NHS R&D
- The Cooksey Review and OSCHR
- Refresh of Bioscience Innovation & Growth Team
- Advanced Therapies Regulation
- Office of Life Sciences to help coordinate this area to improve opportunities in UK Life Sciences sector
- Big Pharma enters arena
- Initiation of clinical trial programmes using stem cell lines earlier than envisaged (eg Tracheal transplant in the EU, ReNeuron trial in the UK and Geron trial in the US)

Thank you

john.connolly@dh.gsi.gov.uk

John Connolly PhD
Cell & Gene Therapies Team
Health, Science & Bioethics Division

DH Department of Health